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COULD RED CELL DISTRIBUTION WIDTH SERVE AS A NEW INFLAMMATORY MARKER IN CORONARY ARTERY BYPASS GRAFTING?

Murat Günday¹, Özgür Çiftçi², Kazım Körez³

Aim. In our study, we researched whether on-pump and off-pump coronary artery bypass grafting (CABG) differ as regards their effect on postoperative red cell distribution width (RDW). Moreover, we also investigated whether there was a link between the preoperative and postoperative RDW levels and the early adverse events after CABG.

Material and methods. In this study there were 127 consecutive patients who had previously undergone CABG. The patients were divided as group 1 (off-pump, n: 49) and group 2 (on-pump, n: 78). The hemogram and biochemistry panel values were measured a day before the operation, on the first, third and seventh days after it, and in the postoperative first and sixth months.

Results. The statistically significant values detected in the hemogram were as follows: postoperative first day hemoglobin, postoperative first day leukocyte, postoperative first day thrombocyte, postoperative first day C-reactive protein, postoperative third day RDW, postoperative third day leukocyte, postoperative seventh day RDW, postoperative seventh day leukocyte, postoperative first month RDW, and postoperative first month thrombocyte ($p < 0.05$). It was found in multivariate analysis that preoperative RDW is an independent risk factor for plasma used in the postoperative period (odds ratio: 0.552; 95% CI: 0.346–0.879; $P = 0.012$). There was no link between preoperative RDW and other early adverse events in the postoperative period ($p > 0.05$).

Conclusion. We found that on-pump CABG increases the RDW levels more in the acute period, when compared with off-pump surgery, but that this effect disappears by the sixth month after the operation. For this reason, RDW can be used as a new

inflammatory marker in patients undergoing CABG. Moreover, we observed that there was no clinical link between early adverse events after CABG and the pre- and postoperative RDW levels.

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Key words: red cell distribution, bypass, on-pump.

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CABG — coronary artery bypass grafting, ICU — intensive care unit, LIMA — left internal mammarian artery, RDW — red cell distribution width.

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МОЖЕТ ЛИ РАСПРЕДЕЛЕНИЕ ЭРИТРОЦИТОВ СЛУЖИТЬ В КАЧЕСТВЕ НОВОГО ВОСПАЛИТЕЛЬНОГО МАРКЕРА ПРИ АОРТОКОРОНАРНОМ ШУНТИРОВАНИИ?

Murat Günday¹, Özgür Çiftçi², Kazım Körez³

Цель. В нашем исследовании мы изучали, могут ли on-pump и off-pump методы при коронарном шунтировании (АКШ), различаться в отношении их влияния на послеоперационную ширину распределения эритроцитов (RDW). Кроме того, мы также исследовали, существует ли связь между предоперационным и послеоперационным уровнями RDW и ранними неблагоприятными событиями после АКШ.

Материал и методы. В этом исследовании было 127 пациентов, которые ранее прошли АКШ. Пациенты были разделены: группа 1 (off-pump, n: 49) и группы 2 (on-pump, n: 78). Значения гемограммы и биохимии крови были измерены в день до операции, на первые, третьи и седьмые сутки после нее и в послеоперационном периоде первого и шестого месяцев.

Результаты. Статистически значимые значения, обнаруженные в гемограмме были следующими: в первый послеоперационный день — гемоглобин, лейкоциты, тромбоциты, С-реактивный белок; третий послеоперационный день — RDW, лейкоциты; седьмой послеоперационный день — RDW, лейкоциты, первый послеоперационный месяц — RDW и тромбоциты ($p < 0.05$). Было обнаружено при многофакторном анализе, что предоперационные RDW являются независимым фактором риска для плазмы, используемой в послеоперацион-

ном периоде (отношение шансов: 0.552; 95% CI: 0.346–0.879; $P = 0.012$). Не обнаружено связи между предоперационными RDW и ранними осложнениями в послеоперационном периоде ($p > 0.05$).

Заключение. Мы обнаружили, что on-pump АКШ увеличивает уровни RDW в более в острый период, когда по сравнению с off-pump хирургией, однако этот эффект исчезает к шестому месяцу после операции. По этой причине, RDW может быть использован в качестве новых воспалительных маркеров у пациентов, перенесших АКШ. Кроме того, мы заметили, что не было никакой клинической связи между ранними неблагоприятными событиями после АКШ и пред — и послеоперационным уровнями RDW.

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Ключевые слова: распределение эритроцитов, bypass, on-pump.

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Introduction

The red cell distribution width (RDW) as measured in blood hemogram expresses the heterogeneity in the volumetric dimensions of the erythrocytes. Originally it is used to distinguish types of anemia. However, it has been recently demonstrated that an increase in the RDW values may be associated with heart failure, coronary artery disease or peripheral artery disease [1–4]. Moreover, RDW is believed to be an indicator of inflammation as well, since

an increase in this value might be a result of oxidative stress on the erythrocytes. RDW deformability may contribute to the impairment of blood flow through the microcirculation. Today, coronary artery bypass grafting (CABG) can be made using either the on-pump or off-pump technique. It is known that on-pump surgery has an inflammatory effect because of hypothermia, the contact of the blood with foreign surfaces outside the body, and laminar flow [5]. On account of this inflammation, many tissues and organ

systems are adversely affected after CABG. Moreover, it is possible for extracorporeal circulation and hemoseparation to cause coupled mechanical and chemical blood trauma, which influences red cell deformability [6].

In this study, we researched whether on-pump and off-pump CABG differ as regards their effect on postoperative RDW. Could RDW serve as a new inflammatory marker in CABG? Moreover, we also investigated whether there was a link between the pre- and postoperative RDW levels and the early adverse events after CABG.

Material and methods

The prospective study we conducted included 127 consecutive patients. The patients were divided as group 1 (off-pump, 38 men, 11 women, n: 49) and group 2 (on-pump, 55 men, 23 women, n: 78). The exclusion criteria were as follows: infection, malignancy, hypo- and hyperthyroidism, chronic renal or hepatic failure, abnormal hemogram, leukocyte or thrombocyte count in the blood, emergencies, patients in cardiogenic shock (preoperative use of high-dose inotropes or of intra-aortic balloon), an ejection fraction of 30 or below as revealed by preoperative echocardiography, coronary endarterectomy, left ventricular aneurysm, mechanical complications of coronary artery disease (post-

myocardial ventricular septal defect, rupture of the ventricular free wall), valvular heart disease, and combined operation involving heart valve surgery and CABG.

The hemogram and biochemistry panel values were measured a day before the operation, on the first, third and seventh days following it, and in the postoperative first and sixth months. An Abbott Cell-Dyn 3700 Hematology Analyzer (Abbott Diagnostics, Santa Clara, CA, and ABD) was used to measure the blood counts. In our laboratory, the normal range for RDW values for healthy persons is between 11.6–15.5%. The primary outcome, the combination of adverse events, included such factors as ventilation time, the amount of drainage, the length of stay in the intensive care unit (ICU), the period of hospitalization, the amount of blood transfusion, atrial fibrillation, acute renal failure, pleural effusion, stroke, sternal infection, pulmonary infection, reoperation due to bleeding, mediastinitis, return to the ICU, and in-hospital death.

The study was conducted according to the principles included in the Declaration of Helsinki on Biomedical Research involving Human Subjects. The informed consent of all patients was obtained beforehand.

Table 1

Results of the analysis of the differences between the two groups as regards the demographic variables

VARIABLES	GROUPS		t/MWU	p
	Group 1	Group 2		
EuroSCORE	2,70±2,11	3,98±2,45	-2,982	0,003*
Average age (years)	60,46±10,19	61,41±8,39	-0,571	0,569
Height (cm)	166,72±9,07	163,89±9,94	1,604	0,111
Weight (kg)	77,05±11,39	77,80±14,32	-0,309	0,758
BMI (kg/m ²) **	19,78±1,83	16,62±1,55	-0,718	0,472
Systolic blood pressure (mmHg)	128,33±11,08	130,09±11,05	-0,624	0,534
Diastolic blood pressure (mmHg) **	75,75±1,88	75,27±1,44	-0,048	0,962
Heart rate (beats/minute)	76,27±7,80	78±7,02	-1,012	0,315
BUN**	18,20±1,35	17,60±0,72	-0,300	0,764
Creatine**	0,90±0,03	0,93±0,03	-0,397	0,691
Fasting blood glucose (mg/dL) **	116,31±7,32	128,40±7,05	-1,898	0,058
Total cholesterol (mg/dL)	181,56±39,80	184,36±42,53	-0,362	0,718
Triglyceride (mg/dL) **	171,31±15,68	167,60±10,41	-0,555	0,579
HDL cholesterol (mg/dL)	38,85±9,33	39,59±8,02	-0,465	0,643
LDL cholesterol (mg/dL)	108,54±33,22	109,27±32,86	-0,120	0,905
Uric acid (mg/dL)	5,31±1,05	5,24 ±1,59	0,242	0,809
CRP (mg/dL) **	5,73±0,88	8,29±1,33	-0,845	0,398
GGT (U/L) **	33,42±4,93	42,11±8,67	-0,818	0,426
Preoperative left ventricular EF (%)	60,39±8,00	61,87±9,46	-0,711	0,479

* — The variables with statistically significant test results ($p < 0,05$); ** — The demographic variables that are subjected to the Mann Whitney-U test as they do not have normal distribution.

Note: In the variables whose change from one group to the other has been measured by Mann Whitney U test, the mean of ordinal numbers has been used instead of the mean value.

Abbreviations: BMI — body mass index, BUN — blood urea nitrogen, CRP — C-reactive protein, EF — ejection fraction, GGT — Gamma glutamil transperase, HDL cholesterol — high density lipoprotein, LDL — low density lipoprotein, MWU — Mann Whitney-U test value.

Table 2

The differences between the two groups in RDW, MPV, thrombocyte, hemoglobin, leukocyte and CRP values during the preoperative period and on the postoperative first, third, and seventh days as well as in the postoperative first and sixth months

VARIABLES	GROUPS		t/MWU	p
	Group 1	Group 2		
Preop. MPV (fL) **	7,74±0,27	7,94±0,12	-0,429	0,668
Preop. RDW (%) **	15,24±0,36	15,51±0,13	-0,266	0,790
Preop. leukocyte (K/μL)	8,53±3,46	7,69±1,84	1,565	0,122
Preop. thrombocyte (K/μL) **	247±6,64	257,21±10,24	-0,151	0,790
Preop. Hb (g/dL)	13,69±2,84	13,45±1,63	0,601	0,596
Preop. CRP (mg/L) **	5,73±0,88	8,29±1,33	-0,845	0,398
Postop. 1 st day MPV (fL) **	8,44±0,17	8,17±0,21	-1,259	0,208
Postop. 1 st day RDW (%) **	15,36±0,15	15,93±0,21	-2,023	0,043
Postop. 1st day leukocyte (K/μL)	10,39±3,71	11,94±3,75	-2,264	0,025
Postop. 1st day Hb (g/dL)	12,15±1,59	11,04±1,34	3,098	0,002
Postop. 1st day thrombocyte (K/μL)	213,45±51,65	178,25±75,74	4,189	0,000
Postop. 1st day CRP (mg/L) **	133,36±15,11	99,35±7,58	-2,471	0,013
Postop. 3 rd day MPV (fL)	8,40±1,14	8,51±1,14	-0,523	0,602
Postop. 3rd day RDW (%)	15,16±1,10	16,05±1,64	-3,373	0,001
Postop. 3rd day leukocyte (K/μL)	8,75±2,90	10,20±3,16	-2,588	0,011
Postop. 3 rd day Hb (g/dL) **	11,29±0,17	11,43±0,28	-0,050	0,960
Postop. 3 rd day thrombocyte (K/μL)	209,94±44,75	177,17±78,32	-0,381	0,704
Postop. 3 rd day CRP (mg/L)	148,99±64,64	130,80±49,66	1,254	0,215
Postop. 7 th day MPV (fL)	7,72±0,78	7,73±1,29	-0,013	0,989
Postop. 7th day RDW (%) **	15,41±0,22	16,07±0,19	-2,697	0,007
Postop. 7th day leukocyte (K/μL)	8,39±2,05	10,13±2,81	-3,176	0,002
Postop. 7 th day Hb (g/dL) **	11,78±0,17	12,33±0,34	-0,811	0,418
Postop. 7 th day thrombocyte (K/μL)	281,58±61,69	273,11±97,79	-1,083	0,281
Postop. 7 th day CRP (mg/L)	63,51±24,65	65,16±26,76	-0,289	0,773
Postop. 1 st month MPV (fL)	7,47±0,95	7,26±0,90	1,167	0,246
Postop. 1st month RDW (%)	15,69±1,00	16,55±1,59	-3,497	0,001
Postop. 1 st month leukocyte (K/μL)	7,92±1,66	7,75±1,63	0,520	0,604
Postop. 1 st month Hb (g/dL)	13,42±1,02	12,99±1,15	-0,139	0,890
Postop. 1st month thrombocyte (K/μL)	339,35±86,62	341,87±97,63	1,997	0,048
Postop. 1 st month CRP (mg/L) **	16,24±3,21	23,46±4,67	-0,285	0,776
Postop. 6 th month MPV (fL)	8,12±1,43	7,94±1,22	0,647	0,519
Postop. 6 th month RDW (%)	16,26±1,11	16,63±1,47	-1,291	0,200
Postop. 6 th month leukocyte (K/μL)	7,30±1,63	7,86±2,24	-1,413	0,161
Postop. 6 th month thrombocyte (K/μL) **	259±11,01	261,07±11,46	-0,310	0,757
Postop. 6 th month Hb (g/dL)	14,68±1,32	14,18±1,28	1,839	0,069
Postop. 6 th month CRP (mg/L) **	4,79±1,40	12,85±3,74	-0,460	0,646

* — The variables with statistically significant test results ($p < 0,05$); ** — The demographic variables that are subjected to the Mann Whitney-U test as they do not have normal distribution.

Note: In the variables whose change from one group to the other has been measured by Mann Whitney U test, the mean of ordinal numbers has been used instead of the mean value.

Abbreviations: CRP — C-reactive protein, Hb — Haemoglobin, MPV — Mean platelet volume, Preop. — Preoperative, Postop. — Postoperative, RDW — Red cell distribution width.

Cardiac Surgery

On-pump surgery: Median sternotomy was applied to each patient under anesthesia. Standard aorta-caval cannulation was used, along with a membrane oxygenator and a roller pump. The patients were routinely cooled off to 28–30°C. The arterial and venous grafts were made ready. For the protection of the myocardium, a cold

crystalloid cardioplegia was used. It was administered every 20 minutes. The anastomoses were first applied to the right coronary artery or its posterior descending branch, then to the circumflex coronary artery branches, afterwards to the diagonal artery, and finally to the left anterior descending (LAD) coronary artery. The left internal mammarian artery (LIMA) was routinely

Table 3

Operative and postoperative data

VARIABLES	GROUPS		t/MWU	p
	Group 1	Group 2		
The number of anastomoses **	2,73±0,11	2,97±0,11	-8,607	0,1117
Ventilation time (hrs) **	6,17±0,65	33,37±15,24	-2,017	0,044*
1 st day drainage amount (ml/24 hrs)	507,45±246,49	498,53±258,72	0,185	0,852
2 nd day drainage amount (ml/24 hrs) **	189,74±21,11	238,88±19,80	-1,646	0,100
3 rd day drainage amount (ml/24 hrs)	133,33±28,87	165,62±158,87	-0,343	0,739
The period of stay in the ICU (days) **	2,88±0,36	2,53±0,11	-1,153	0,249
The period of hospitalization (days) **	4,56±0,29	8,28±0,49	-6,697	0,000*
ERT (units) **	2,23±0,43	2,46±0,19	-1,333	0,182
Full blood (units) **	1,48±0,12	3,35±0,18	-5,947	0,000*
Plasma (units) **	3,81±0,28	5,42±0,29	-3,752	0,000*

* — The variables with statistically significant test results ($p < 0,05$); ** — The demographic variables that are subjected to the Mann Whitney-U test as they do not have normal distribution.

Note: In the variables whose change from one group to the other has been measured by Mann Whitney U test, the mean of ordinal numbers has been used instead of the mean value.

Abbreviations: ERT — erythrocyte suspension, hrs — hours.

Table 4

Postoperative early adverse events

VARIABLES	GROUPS		x	p
	Group 1	Group 2		
AF 0 1	44 5	60 14	1,714	0,214
Pleural effusion 0 1	49 0	64 10	7,208	0,006*
ARF 0 1	48 1	73 1	0,088	1,000
Sternal infection 0 1	49 0	70 4	2,738	0,150
Pulmonary infection 0 1	48 1	71 3	0,380	1,000
Reoperation due to bleeding 0 1	49 0	73 1	0,668	1,000
Mediastinitis 0 1	49 0	73 2	1,328	0,518
Return to the ICU 0 1	49 0	73 5	3,270	0,156

* — The variables with statistically significant test results ($p < 0,05$).

Note: Since the values in the cells turned out to be 5 or less in the observed frequencies, the results of Fisher's Exact test were used when determining whether there was a correlation between the variables.

Abbreviations: AF — atrial fibrillation, ARF — acute renal failure, ERT — erythrocyte suspension, ICU — intensive care unit.

extracted to use for the LAD artery anastomosis. The proximal anastomoses were applied to the aorta under a side clamp.

Off-pump surgery: The chest was opened using median sternotomy. The arterial and venous grafts were made ready. The heart was suspended with pericardial sutures. Then, Octopus Tissue Stabilizers (Medtronic) were used to immobilize the location where distal anastomosis was going to be applied. In those cases that necessitated the anastomoses to be applied to the rear side of the heart, a starfish (Medtronic) was used to position the heart. Following arteriotomy, a coronary shunt (Medtronic) appropriate for the coronary diameter was fitted. The distal and proximal anastomoses were applied as described above. The pericardium was not closed in any of the patients (on-pump or off-pump).

Statistical analysis. We divided all the variables in the study into two groups, on-pump and off-pump, and examined whether there was any difference between these groups as regards the variables in question. For this examination, the Kolmogorov-Smirnov normality test was used to determine whether the variables to be used in the analyses had normal distribution. When testing the differences between the groups, the Independent Samples T Test (Student t test) was used for the variables with normal distribution, and Mann Whitney-U test, a nonparametric test, was used for those variables without normal distribution. A significance level of 5% was taken into account during the evaluation of the analyses. On the other hand, the Chi-square test was used when examining the association of our dependent variable (i.e. whether the group had undergone on-pump or off-pump surgery) with the categorical variables. Since the values observed in the Chi-square test were less than or equal to 5, the results of Fisher's exact test were evaluated. In the second part of our analyses, we used Logistic Regression Analysis to determine which variables affected RDW and which do not. We selected the variables in the Logistic Regression

Table 5

The results of multiple Logistic Regression Analysis for the dependent variable: preoperative RDW

VARIABLES	Univariate Analysis			Multivariate Analysis		
	OR	95%CI	p	OR	95%CI	p
Full blood (units)	0,895	0,698–1,147	0,379			
Plasma (units)	0,918	0,789–1,070	0,274	0,552	0,346–0,879	0,012*
AF	1,256	0,470–3,353	0,649	8,105	0,764–86,016	0,083
Pleural effusion	0,889	0,238–3,325	0,861			
Sternal infection	0,438	0,044–4,334	0,480			
Pulmonary infection	0,438	0,044–4,334	0,480			
Return to the ICU	5,680	0,616–52,349	0,125			
Ventilation time (hrs)	0,999	0,995–1,003	0,685			
1st day drainage amount (ml/24 hrs)	1,000	0,999–1,002	0,716			
2nd day drainage amount (ml/24 hrs)	0,999	0,996–1,002	0,525	1,006	0,999–1,012	0,090
ERT (units)	0,945	0,657–1,359	0,760			

* — The variables with statistically significant test results ($p < 0,05$).

Abbreviations: AF — atrial fibrillation, CI — confidence interval, ERT — erythrocyte suspension, hrs — hours, ICU — intensive care unit, OR — odds ratio.

Table 6

The results of multiple Logistic Regression Analysis for the dependent variable: first month RDW

VARIABLES	Univariate Analysis			Multivariate Analysis		
	OR	95%CI	p	OR	95%CI	p
Full blood (units)	1,099	0,818–1,476	0,533	0,234	0,060–0,914	0,037*
Plasma (units)	1,092	0,922–1,293	0,310	2,257	1,004–5,078	0,049*
AF	9,250	1,166–73,364	0,035*			
Pleural effusion	1,687	0,324–8,801	0,535			
Sternal infection	1,657	0,166–16,500	0,667			
Pulmonary infection	1,088	0,095–12,406	0,946			
Return to the ICU	2,114	0,228–19,608	0,510			
Ventilation time (hrs)	1,000	0,995–1,004	0,869			
1 st day drainage amount (ml/24 hrs)	1,000	0,999–1,002	0,765	1,011	1,001–1,020	0,026*
2 nd day drainage amount (ml/24 hrs)	0,999	0,996–1,002	0,696	0,988	0,976–1,001	0,066
ERT (units)	1,288	0,799–2,077	0,299	0,215	0,045–1,019	0,053

* — The variables with statistically significant test results ($p < 0,05$).

Abbreviations: OR — odds ratio, CI — confidence interval, AF — atrial fibrillation, ICU — intensive care unit, ERT — erythrocyte suspension, hrs — hours.

Analysis through the backward selection method. Taking the first and last (eighth) steps in the eight-step results, according to the backward selection method, we determined the variables affecting the dependent variable. In the model containing all the variables, and finally among the variables obtained through the backward method, we determined the variables affecting the RDW value. Since the RDW values were the results of measurements made at six different points in time, we applied logistic regression for every subgroup, while we did not include those models in which none the variables had any effect. The statistics program IBM SPSS 21 was used to calculate all the statistical results.

Results

The average age was 60.46 ± 10.19 in group 1 and 61.41 ± 8.39 in group 2. We did not need to use intra-aortic balloon pump and/or high-dose inotropes in any

of our patients, as would be necessitated by low postoperative ventricular performance. In-hospital mortality (the first 30 days) was not encountered either. Demographically, there was no difference between the two groups with the exception of EuroSCORE (Table 1). The statistically significant values detected in the hemogram were as follows: postoperative first day hemoglobin, postoperative first day leukocyte, postoperative first day thrombocyte, postoperative first day C-reactive protein, postoperative third day RDW, postoperative third day leukocyte, postoperative seventh day RDW, postoperative seventh day leukocyte, postoperative first month RDW, and postoperative first month thrombocyte ($p < 0.05$) (Table 2).

Examining the operative and postoperative data, a statistically significant difference was detected between the two groups as regards the ventilation time, the period of hospitalization, and the use of full blood and plasma

($p < 0.05$) (Table 3). As for the adverse events in the early postoperative period, a significant difference in pleural effusion was detected between the two groups ($p < 0.05$) (Table 4). It was found in multivariate analysis that preoperative RDW is an independent risk factor for plasma used in the postoperative period (odds ratio: 0,552; 95% CI: 0,346–0,879; $P = 0,012$). There was no association between preoperative RDW and other early adverse events in the postoperative period (Table 5).

It was found that postoperative first month RDW constitutes an independent risk factor for full blood used in the postoperative period (odds ratio: 0,234; 95% CI: 0,060–0,914; $P = 0,037$), plasma (odds ratio: 2,257; 95% CI: 1,004–5,078; $P = 0,049$) and postoperative first day drainage (odds ratio: 1,011; 95% CI: 1,001–1,020; $P = 0,026$). It was not associated with any other early adverse events (Table 6). Moreover, no significant correlation was found between postoperative early adverse events and any of the RDW values on the first, third and seventh days and in the sixth month ($p > 0,05$).

Discussion

To our knowledge, this study shows for the first time in the literature that the RDW levels of the patients undergoing on-pump surgery increase more in the early postoperative period, compared with the RDW levels of the off-pump patients, and that this difference in the respective effects of the two techniques diminishes by the sixth month after the operation. We believe that the reason for this is the triggering effect of cardiopulmonary bypass on inflammation. In addition, the study revealed that there was no statistically significant difference between the two groups as regards early adverse events, and that there was no clinical link in the correlation analysis between the pre- and postoperative RDW levels on the one hand, and early adverse events following surgery on the other.

It is possible to observe elevated RDW levels in many clinical settings including hemolysis, blood transfusions and ineffective red cell production due to the deficiency of iron, vitamin B12 or folate. RDW levels may also rise in such clinical states as pregnancy, thrombotic thrombocytopenic purpura and inflammatory bowel diseases. However, its use in the clinic is generally neglected [7]. Various studies have revealed that high RDW values may lead to an increase in adverse cardiovascular events and even mortality in people with heart failure or coronary artery disease [1, 2].

Although the mechanisms that underlie this link remain unclear, it is possible that red blood cell (RBC) deformability has a contributing effect. There is a link between greater variation in RBC volumes (increased RDW) and decreased RBC deformability, which can lead to impairment of blood flow through the microcirculation [8]. (The mechanism underlying this phenomenon is not fully known. It is thought that high RDW levels possibly

impair the microcirculation). It has been found that increased RDW values are associated with some inflammatory markers [9, 10]. It has also been shown to be linked with arterial and venous thrombosis, an association that might stem from increased inflammation [11, 12].

In the literature, there are few studies on the link between CABG and RDW. The preoperative RDW has been found to be associated with atrial fibrillation beginning after CABG [13]. Another study has revealed that the RDW constitutes a significant factor that determines the ratio of in-hospital mortality and long-term survival in patients undergoing isolated CABG [14]. In their study, Ertekin Utku Unal et al. showed that there is an association between higher RDW values and early adverse events following CABG surgery [15]. Another study has found an independent association between elevated RDW and recourse to CABG. [16]. In almost all of the studies above on RDW and CABG, the RDW values used have been obtained in the preoperative period only, while no such values are present that pertain to the period after surgery.

There is a link between CABG surgery and systemic inflammation. The activation of neutrophils constitutes a crucial step in inflammation, and leads to neutrophil sequestration within the tissues. Among the potential advantages of off-pump CABG surgery is that it allows for the attenuation of the systemic inflammatory response [17]. In another study, coronary revascularization with cardiopulmonary bypass (CPB) led to a significantly higher level of TNF-alpha, which was linked with P-selectin and ICAM-1 expression. This was accompanied by a requirement for higher catecholamine in the CPB group during the early postoperative period. Although the surgical trauma involved in on-pump and off-pump surgery is comparable, the off-pump technique, dispensing with CPB and cardioplegic arrest, allows for a significant reduction in systemic and cardiac adhesion molecule expression as well as in catecholamine requirement [18].

We did not encounter any previous studies on the effects of on-pump and off-pump CABG on RDW. In this study we found that on-pump CABG increases the RDW levels more in the acute period, compared with off-pump surgery, but that this effect disappears by the sixth month after the operation. We believe that the reason for this is the triggering effect of cardiopulmonary bypass on inflammation. Moreover, we observed that there was no clinical link between early adverse events after CABG and the pre- and postoperative RDW levels.

Conclusion

Many previous studies using the basic inflammatory markers have shown that off-pump bypass surgery prevents the secondary inflammatory response that develops after on-pump bypass surgery [19–21]. In our own study, we have found that RDW can be used as a new inflammatory

marker in patients who have undergone CABG. Determining RDW is easy and brings no extra costs as it is measured in many health centres as part of the routine hemogram examination. According to the results of our study, it can be used as a new inflammatory marker in patients who have undergone CABG. We believe that on this subject there is a need for further prospective, double-blinded and randomized studies with a larger number of patients.

Study limitations

This was an inherently retrospective observational study that included only a small number of patients. The clinical significance of RDW was not clear in CABG. This is a preliminary study and needs further randomized or large volume study. Moreover, the changes in RDW should also be examined in surgeries associated with other cardiological pathologies.

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ANALYSIS OF RENAL FUNCTION AFTER ON AND OFF PUMP CORONARY ARTERY BYPASS GRAFTING

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Cardiopulmonary bypass (CPB) is often associated with renal dysfunction, as measured by plasma creatinine levels and hemodialysis rates.

Aim. To compare creatinine clearance (CrCl), estimated with the Cockcroft and Gault formula, between patients undergoing off-pump coronary artery bypass grafting (OPCAB) versus on-pump CABG (on-CAB).

Material and methods. Between April 2008 and April 2009, 119 patients underwent coronary bypass graft surgery. Fifty-eight (58) of these patients underwent OPCAB while 61 had on-CAB. Creatinine clearance, plasma creatinine levels, and clinical outcome were compared between the groups. A creatinine clearance value of 50 mL/minute was accepted as the lowest limit of normal renal function.

Results. There were two hospital deaths caused by sepsis after pulmonary infection. Creatinine clearance (Preoperative OPCAB 73.64 ± 33.72 x on-CAB 75.70 ± 34.30 mL/min; discharge OPCAB 75.73 ± 35.07 x on-CAB 79.07 ± 34.71 mL/min; $p=0.609$), and creatinine levels (Preoperative OPCAB 1.04 ± 0.38 x on-CAB 1.13 ± 0.53 mg/dL; discharge OPCAB 1.12 ± 0.79 x on-CAB 1.04 ± 0.29 mg/dL; $p=0.407$) did not show statistically inter-group differences.

Conclusion. Deterioration in renal function is associated with higher rates of postoperative complications. No significant difference in CrCl could be demonstrated between the groups.

Key words: coronary artery bypass, kidney, off-pump coronary artery bypass, bypass surgery, coronary artery.

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АНАЛИЗ ФУНКЦИИ ПОЧЕК ПОСЛЕ ON-PUMP И OFF-PUMP АОРТОКОРОНАРНОГО ШУНТИРОВАНИЯ

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Кардиопульмонарное шунтирование (CPB) часто ассоциируется с дисфункцией почек, как следует из анализа уровней креатинина в плазме и уровней гемодиализа.

Цель. Сравнить клиренс креатинина (CrCl), рассчитанного по формуле Кокрофта-Голта, у пациентов, перенесших off-pump коронарное шунтирование (OPCAB) и on-pump коронарное шунтирование (on-CAB).

Материал и методы. В период с апреля 2008 г. по апрель 2009 г., 119 пациентов, были подвергнуты коронарному шунтированию. Пятьдесят восемь (58) из этих пациентов прошли OPCAB, в то время как 61 — (on-CAB). Клиренс креатинина, уровень креатинина плазмы, и клинические результаты сравнивались между группами. Значение клиренса креатинина 50 мл/мин было принято в качестве минимального предела нормальной функции почек.

Результаты. Были два смертельных случая в больнице, вызванных сепсисом после легочной инфекции. Клиренс креатинина (предоперационная OPCAB 73.64 ± 33.72 x on-CAB 75.70 ± 34.30 мл/мин; постоперационная величина OPCAB 75.73 ± 35.07 x on-CAB 79.07 ± 34.71 мл/мин; $p=0.609$) и уровни креатинина (предоперационная OPCAB 1.04 ± 0.38 x on-CAB 1.13 ± 0.53 мг/дл; постопе-

рационное значение OPCAB 1.12 ± 0.79 x on-CAB 1.04 ± 0.29 мг/дл; $p=0.407$) не имеют статистических различий между группами.

Заключение. Ухудшение функции почек ассоциируется с более высокой частотой послеоперационных осложнений. Существенной разницы в значениях уровня креатинина, не может быть продемонстрировано между группами.

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Ключевые слова: аорто-коронарное шунтирование, почки, off-pump аорто-коронарное шунтирование, хирургия, коронарная артерия.

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Introduction

Among cardiovascular surgeries, coronary artery bypass surgery, also coronary artery bypass graft (CABG) surgery, and colloquially heart bypass or bypass surgery is a surgical procedure performed to relieve angina and reduce the risk of death from coronary artery disease [1–4]. Deterioration of renal function after heart surgery is associated with increased morbidity and mortality. Its incidence may vary from 8% to 30% of cardiopulmonary bypass (CPB) operations and is associated with a mortality rate between 7% and 38% [5, 6]. Previous studies with patients

undergoing CPB showed significant increases in plasma levels of creatinine, with consequent acute renal failure and need for hemodialysis [7, 8].

Plasma creatinine values may not represent a specific marker of renal dysfunction, since it can be affected by muscle mass and sex. Moreover, we can see significant reductions in glomerular filtration rates with normal plasma creatinine levels [9,10]. Creatinine clearance (CrCl) can be estimated by the formula developed by Cockcroft and Gault; its value is more associated with renal dysfunction and morbidity and postoperative mortality [11,12].

In 2007, Sajja LR et al. published a study comparing coronary artery bypass grafting (CABG) with and without CPB in patients with renal failure not on dialysis preoperatively and demonstrated a favorable effect on renal function in the off-pump operation, with more benefits pronounced in patients with diabetes mellitus (DM), hypertension (HBP), and those with greater impairment of ventricular function [13]. Other studies have compared CABG with and without CPB in order to demonstrate the deleterious effect of CPB on renal function; however, many did not use CrCl as a marker of renal dysfunction [14,16]. The increase in severity of cases referred for CABG makes surgery without CPB a useful tool to decrease morbidity and operative mortality.

The objective of this study is to test the effect of CPB on renal function in patients undergoing coronary artery bypassgrafting(CABG),withandwithoutcardiopulmonary bypass, through creatinine clearance calculated by the Cockcroft and Gault formula.

Material and methods

Between April 2007 and April 2009, 119 patients with heart failure and indication for CABG were divided into two groups (off-pump and on-pump groups, which were randomly selected). The randomization was based on a random number generator. The measurement parameters needed to calculate the CrCl preoperatively and at discharge were done. The study protocol was approved by the institutional Ethics and Research Committee and the patients agreed to participate by signing an informed consent.

Exclusion criteria were: chronic renal failure requiring dialysis, left ventricular ejection fraction (LVEF) below 30%, associated cardiac surgery beside CABG, minimally invasive operation, and urgent or emergency operation.

Clinical and demographic pre-operative characteristics are shown in Table 1.

Anesthesia and surgical technique

The operation began with hemodynamic monitoring, with measurement of mean arterial pressure, central venous pressure and urine output, and respiratory monitoring with pulse oximetry.

Anesthetic induction was performed with midazolam (100–200µg/kg), fentanyl(150–200mg), and pancuronium (50–100 mg/kg), and maintained with propofol (5–10 mg/kg/hour). The operation was carried out as usual, the means of access being by median sternotomy with cannulation of the aorta and inferior vena cava through the right atrium after systemic heparinization (300UI/Kg), obtaining an activated clotting time (ACT) above 480s, with mild hypothermia to 34 °C. In patients operated without CPB, systemic heparinization was done (150UI/Kg) with ACT above 250s and use of mechanical suction stabilizer during construction of anastomoses.

The method of myocardial protection used was controlled hypoxia with intermittent aortic clamping,

which was done to perform the anastomoses between the coronary arteries and bypass grafts that would likely be chosen (left internal mammary artery or saphenous vein).

At the end of surgery, the patients in normothermia were taken to the postoperative unit, where they were continuously monitored.

Patient follow-up was done by a single member of the surgical team, who followed a protocol for pre- and post-operative comparison.

Calculation of creatinine clearance

The creatinine plasma levels were routinely obtained in all patients in the preoperative period and before hospital discharge. These values were used to estimate CrCl by the Cockcroft and Gault formula, with correction for sex and weight of the patient. The Cockcroft and Gault equation is expressed as follows: male- $[140 - \text{age (years)}] \times \text{weight (kg)} / 72 \times \text{serum creatinine}$, and female- $140 - \text{age (years)}] \times \text{weight (kg)} / 72 \times 0.85 \times \text{serum creatinine}$. The age is in years, weight in kilograms and plasma creatine in micromoles per milliliter. The value of 50ml/min CrCl was accepted as the lower limit of normal renal function.

Statistical analysis

In order to verify the minimal number of patients investigated to provide statistical or no statistical significance, we applied the power analysis that provided a minimal number of 100 subjects. The choice of measures of central tendency and dispersion of the values that make up the samples and the statistical tests for comparison between them were based on the type of distribution, defined as parametric by the Kolmogorov-Smirnov test, according to the statistical program SPSS® version 13.0 (SPSS ® Inc, Illinois, USA). The values obtained for the study of each continuous variable were organized and expressed as means and standard deviations. For the categorized variables, absolute and relative frequencies were used. To compare the means of two sample populations, we used the Student “t” test and, between the paired means, we used the paired t-test. To verify the existence of correlation between two continuous variables, we used the Pearson correlation test.

Results

There were two deaths due to lung infection followed by sepsis. The groups were homogeneous in the comparison between the clinical and demographic pre-operative characteristics. The mean CPB time was $49,90 \pm 17,98$ minutes and anoxia was $49,83 \pm 18,45$ minutes. Deterioration in renal function was associated with higher rates of postoperative complications.

The CrCl (preoperative OPCAB $73,64 \pm 33,72$ x on-CAB $75,70 \pm 34,30$ mL/min; discharge OPCAB $75,73 \pm 35,07$ x on-CAB $79,07 \pm 34,71$ mL/min; $p=0,609$) and creatinine plasma levels (preoperative OPCAB $1,04 \pm 0,38$ x on-CAB $1,13 \pm 0,53$ mg/dL; discharge OPCAB $1,12 \pm 0,79$ x on-CAB

Table 1

Demographic and clinical characteristics of patients

Variables	Group W/OUT CPB (n=58)	Group W/CPB (n=61)	p
Gender			0,408
Male	55,2%	75,4%	
Female	44,8%	24,6%	
Age	66,9± 9,10	60,9± 9,5	0,102
HTN	96,6%	93,4%	0,438
COPD	6,9%	11,5%	0,389
DM	53,4%	47,5%	0,519
DLP	48,3%	39,3%	0,326
Smoking	41,4%	65,6%	0,080
Obesity	22,4%	32,8%	0,206
Non-dialytic CRF	13,8%	23,0%	0,198
Previous AMI	62,1%	59,0%	0,733
Uni/biarterial lesion	66,6%	33,4%	0,318
Triarterial lesion	47,6%	52,4%	0,415
LVEF>45%	56,4%	64,7%	0,424
45< LVEF >35	28,2%	23,5%	0,614
LVEF <35%	15,4%	11,8%	0,617

Abbreviations: CPB – cardio pulmonary bypass, HTN – hypertension, COPD – chronic obstructive pulmonary disease, DM – diabetes mellitus, CRF – chronic renal failure, AMI – acute myocardial infarction, LVEF – left ventricular ejection fraction.

Table 2

Creatinine clearance and plasma creatinine levels

Variables	Group W/OUT CPB (n=58)	Group W/CPB (n=61)	p
Cr/Cl (ml/min)			
Preoperative	73,64±33,73	75,70±34,0	0,746
Discharge	75,74±35,07	79,07±34,1	0,609
Plasma creatinine (mg/dL)			
Preoperative	1,04±0,39	1,13±0,54	0,258
Discharge	1,12±0,80	1,04±0,29	0,447

Abbreviations: CPB – cardio pulmonary bypass, CrCl – creatinine clearance.

1,04±0,29mg/dL; $p=0,407$) showed no statistically significant difference between the two groups during both observation periods (pre-operative and discharge) (Table 2).

Discussion

This investigation was undertaken to evaluate creatinine clearance (CrCl), estimated with the Cockcroft and Gault formula, between patients undergoing off-pump coronary artery bypass grafting (OPCAB) versus on-pump CABG (on-CAB). As a main result, we suggest that CABG with CPB did not produce changes in renal function, which was estimated by calculation of CrCl in comparison with the procedure done without CPB.

Renal disorders are recognized as an independent risk factor for increased cardiovascular morbidity and mortality in subjects with heart failure [17, 18]. Previous evidences also suggest that subjects with damaged kidney function are at increased risk for heart failure development [19, 20].

The evaluation of renal function solely by plasma creatinine has limitations, because this parameter may

vary according to age, sex, muscle mass, metabolism, and hypertension [21]. The CrCl is a useful alternative for measurement of the glomerular filtration rate and its direct measurement is not available in clinical practice, so the adoption of formulas for estimating these values is an acceptable solution [22]. Among these formulas, the Cockcroft-Gault equation uses the available clinical data and can be related to heart disease [11, 23]. Renal function remains an important factor that can contribute to hospital mortality rates following open heart surgery, since in more serious situations, which may require dialysis, morbidity and mortality increase significantly regardless of the intensive support offered to patients in this severe clinical condition [24]. Chertow et al. demonstrated a mortality rate of 63% in 30 days in patients who required dialysis, versus 4,3% in the absence of renal dysfunction [25]. Most of the factors responsible for deterioration of renal function postoperatively are inherent to the patient and difficult to control; probably the only preventable factor is whether or not CPB are used.

Despite the continued interest in off-pump CABG techniques, their benefits regarding the degree of renal dysfunction remains controversial. Studies show reduced risk of renal failure, especially in high risk patients, although other studies failed to demonstrate this favorable effect [13, 26, 27]. Shroff GR et al., analyzing the results of hemodialysis patients undergoing CABG, found a modest increase in survival for patients operated without CPB; this increase is more pronounced in the early periods and tends to decrease over the years [28, 29].

In this study, we evaluated the possible deleterious effects of CPB on the renal function of patients undergoing CABG by the estimated CrCl instead of measuring plasma creatinine levels, as previously published studies have shown a higher relationship of CrCl with renal dysfunction (especially in patients with normal serum creatinine) [5, 12]. Our initial hypothesis was that patients operated upon without CPB would have a lower degree of renal dysfunction, as assessed by CrCl. However, our results showed no significant difference when comparing the groups and the same trend occurred with plasma levels of creatinine. This finding is in agreement with other previously published works; this suggests the need for other markers to determine the impact of CPB on renal function, since the CrCl may be normal despite the presence of renal dysfunction, especially when the change in plasma creatinine is mild or moderate [5, 9, 18, 30].

In 2009, Felicio et al. proposed the estimation of the glomerular filtration rate by measurement of serum cystatin C instead of estimated CrCl; major changes of this marker were found post-surgically when CPB was compared with the values of plasma creatinine and estimated CrCl [31].

Against to our data, a previous study [32] reported that acute renal injury after CABG was related to increased long-term risk of heart failure onset. The authors also found that acute renal injury was an independent predictor of hospitalization for heart failure, even after adjustment for confounders that are usually involved in heart failure. We believe that the use of CABG with CPB was able to attenuate a possible acute renal injury. On the other hand,

Nezami and coworkers [33] reported that renal function evaluated with CrCl and Cr after CABG was not significantly distinct between subjects undergoing off-pump and on-pump methods. The alterations in renal function after the both procedures were not associated with the levels of high-sensitivity nor C-reactive protein tumor necrosis factor- α .

Our study presents some limitations that are worth to be addressed. For instance, the potential of a type II statistical error in a negative study with relatively small number of patients. We investigated only heart failure patients; there were no other cardiovascular disorder, since that was not the purpose of our study.

Our surgeon team considered the strategy to proceed with off-pump CABG procedure only when the hemodynamic situation was unstable. All of the procedures were performed in our group is through a median sternotomy approach and under general anesthesia. Previous studies indicated that surgeon experience plays a role and emphasized the importance of surgeon volume in establishing favorable outcomes for off-pump CABG [34, 35]. Based on our experience, we observe a significant surgeon volume—result connection for mortality after off-pump CABG, indicating that high volume of procedures presents better mortality outcomes, we believe that this is due to the experience of the surgeon.

This study investigated the relationship between cardiac surgery procedures and the kidney in the context of CABG with CPB. This is a clinically relevant issue due to the great number of patients that undergo CABG with CPB and due to the high incidence of acute renal function as a perioperative complication. Our study collaborates to the comprehension of cardiac and renal interaction by indicating that acute injury to the renal activity may be induced by cardiac surgery.

Conclusion

We suggest that CABG with CPB did not produce changes in renal function estimated by calculation of CrCl in comparison with the procedure done without CPB.

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CLINICAL ANALYSIS OF ASSOCIATION OF CYSTATIN C AND ATRIAL FIBRILLATION

Ping Liu, Shujian Sui, Dongling Xu

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. 235 paroxysmal and persistent AF (AF1 group) and 254 permanent AF (AF2 group) patients in AF group and 221 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 0,614, 0,520, 0,463 and 0,538 (all $P < 0,01$), but negatively associated with LVEF ($r = -0,356$, $P = 0,012$) in AF group. (3) Multivariate regression analysis showed the hsCRP, cystatin C, LAD and LVEF entered finally into the regression equation (cystatin C, OR: 3.25, 95%CI: 1.05–10.17, $P = 0,008$).

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 АССОЦИИ 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. 235 пациента с пароксизмальной и персистирующей ФП (ФП1 группа), 254 пациента с постоянной ФП (ФП2 группа) и 221 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 LVD 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 давлени-

ем (САД) и креатинином, коэффициенты корреляции были, соответственно, 0,614, 0,520, 0,463 and 0,538 ($P < 0,01$), но отрицательно ассоциированы с ФВ ЛЖ ($r = -0,356$, $P = 0,012$) 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: 3.25, 95%CI: 1.05–10.17, $P = 0,008$).

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: цистатин С, фибрилляция предсердий, воспаление, маркеры воспаления.

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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 increase 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.

Material and methods

Patients

A total of 710 consecutively hospitalized patients with AF (assigned to group AF) were prospectively recruited between June 2008 and December 2010 from the Second Hospital of Shandong University and Qilu Hospital of Shandong University, which included 235 cases of paroxysmal and persistent AF (placed to group AF1), 121 males and 114 females with mean age of $67,42 \pm 12,29$ years old. There were 254 cases of permanent AF (put to group AF2), 129 males and 125 females, averaged ($68,15 \pm 11,52$) years old. All cases of AF diagnosed were verified by medical history, physical examination, electrocardiogram or dynamic electrocardiogram. The control group had 221 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 113 male cases, 108 female cases with a mean age of $66,70 \pm 12,18$ years old. Electrocardiogram showed sinus rhythm in control group. There were not any 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 anemia; intracranial hemorrhage; liver and renal abnormal function and other organs dysfunction; immune system and endocrine metabolic diseases; pregnant women and breastfeeding women; on 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 ethylenediamine tetraacetic acid (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, total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, triglycerides, blood urea nitrogen and serum creatinine 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 ventricular ejection fraction (LVEF) were recorded using a Philips iE33 ultrasonocardiograph (Philips Medical Systems, Bothell, WA, USA).

Statistical treatment

Continuous variables were expressed as mean $\pm$ 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 Table 1. Compared with control group, AF1 and AF2 groups did not have statistical significance in age, gender, triglycerides, total cholesterol and high-density lipoprotein cholesterol ($P > 0,05$), but had higher values of BM, systolic blood pressure, fasting blood glucose and serum creatinine ($P < 0,05$ or $P < 0,01$). Values of blood urea nitrogen and low-density lipoprotein cholesterol were significantly higher whereas those of diastolic blood pressure were significantly lower in group AF2 than in control group. While there were not any significant differences in the values of blood pressure, blood urea nitrogen and low-density lipoprotein cholesterol between group AF1 and control group ($P > 0,05$). Furthermore there were not any

Table 1

Comparison of baseline data between atrial fibrillation and control groups

Variables	control group	group AF1 (paroxysmal and persistent)	group AF2 (permanent)
Number of cases	221	235	254
Age (year)	66,70±12,18	67,42±12,29	68,15±11,52
Male (n, %)	113 (51,13)	121 (51,48)	129 (50,79)
Body mass index (kg/m ²)	26,31±4,38	28,41±4,77*	28,96±5,08*
Systolic blood pressure (mmHg)	132,34±13,26	143,60±14,29*	144,21±15,75*
Diastolic blood pressure (mmHg)	82,91±10,68	79,65±11,32	78,81±11,06*
Fasting blood glucose (mmol/l)	5,86±1,24	6,25±2,20*	6,35±2,44**
Blood urea nitrogen (mmol/l)	5,94±2,27	6,31±3,08	6,58±3,13**
Creatinine (umol/l)	60,78±12,56	87,61±25,80*	88,23±26,40**
Triglycerides (mol/l)	1,18±0,54	1,21±0,48	1,24±0,59
Total cholesterol (mol/l)	4,45±0,86	4,37±0,78	4,50±0,71
High-density lipoprotein (mol/l)	1,32±0,34	1,26±0,29	1,21±0,31
Low-density lipoprotein (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	group AF1	group AF2
White blood cell count ($\times 10^9/L$)	5,88±1,85	6,09±1,92	6,13±2,04
hsCRP (mg/l)	1,27±1,08	2,75±1,17**	3,91±1,24** [#]
cystatin C (mg/l)	0,84±0,16	1,06±0,29*	1,35±0,42** [#]

Abbreviations: AF – atrial fibrillation, hsCRP – high sensitivity C reactive protein. Compared with control group, * $P<0.05$, ** $P<0.01$; Compared with AF1 group, [#] $P<0.05$, ^{##} $P<0.01$

Table 3

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

Variables	control group	group AF1	group AF2
left atrial diameter (mm)	33,67±3,39	43,56±10,64**	47,10±11,72** [#]
Left ventricular diameter (mm)	49,50±7,34	52,64±11,30*	54,15±11,36** [#]
Left ventricular ejection fraction (%)	54,83±8,51	50,08±10,52*	47,36±12,14** [#]

Abbreviation: AF – atrial fibrillation, Compared with control group, * $P<0.05$, ** $P<0.01$; Compared with AF1 group, [#] $P<0.05$, ^{##} $P<0.01$

statistical differences in baseline datum between group AF1 and group AF2 (all $P>0,05$).

Comparison of inflammatory indicators between AF and control groups

As shown in Table 2, white blood cell counts showed no any 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 group AF2 had higher values of cystatin C and hsCRP than those in group AF1 ($P<0,05$ or $P<0,01$).

Comparison of echocardiogram parameters between AF and control groups

As outlined in Table 3, Echocardiogram showed AF1 and AF2 groups had higher values of left atrial diameter and left ventricular diameter but lower values of left ventricular ejection fraction than those of control group

Table 4
Analysis for correlation between cystatin C and high risk factors of atrial fibrillation

Variables	<i>r</i>	<i>P</i>
High sensitivity C reactive protein	0,614	0,000
Left atrial diameter	0,520	0,000
Left ventricular diameter	0,247	0,043
Left ventricular ejection fraction	-0,356	0,012
Systolic blood pressure,	0,463	0,005
Fasting blood glucose	0,219	0,047
Serum creatinine	0,528	0,008
Body mass index	0,187	0,054
Low-density lipoprotein cholesterol	0,165	0,039

($P<0,05$ or $P<0,01$). Compared with group AF1, group AF2 had higher values of left atrial diameter and left ventricular diameter but lower values of left ventricular ejection fraction ($P<0,05$ or $P<0,01$).

Table 5

Multiple logistic regression analysis of predictive factors for atrial fibrillation

Variables	β	SE	OR	P	95%CI
High sensitivity C reactive protein	0,72	2,89	3,74	0,014	1,17–13,84
Cystatin C	0,61	2,36	3,25	0,008	1,05–10,17
Left atrial diameter	0,35	1,14	1,86	0,036	0,92–5,64
Systolic blood pressure	0,59	0,90	1,79	0,005	1,07–4,38
Left ventricular ejection fraction	0,55	0,84	1,27	0,044	0,75–3,09

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, left atrial diameter, systolic blood pressure and serum creatinine, and their correlation coefficient respectively were 0,614, 0,520, 0,463 and 0,528 (all $P < 0,01$) whereas cystatin C was inversely related to left ventricular ejection fraction ($r = -0,356$, $P = 0,012$).

Multivariate Analysis of AF risk factors

As presented in Table 5, all selected variables from AF and control groups were analyzed by stepwise regression analysis and the related indicators were picked out. Finally, hsCRP, cystatin C, left atrial diameter, systolic blood pressure and left ventricular ejection fraction by turns entered the regression equation, showed in Table 5, hsCRP (OR: 3.74; 95% CI: 1.17–13.84; $P = 0,014$), cystatin C (OR: 3.25; 95% CI: 1.05–10.17; $P = 0,008$), left atrial diameter (OR: 1.86; 95% CI: 0.92–5.64; $P = 0,036$), systolic blood pressure (OR: 1.79; 95% CI: 1.07–4.38; $P = 0,005$) and left ventricular ejection fraction (OR: 1.27; 95% CI: 0.82–3.08; $P = 0,044$) included respectively.

Discussion

Cystatin C is a cysteine protease inhibitor with a molecular weight of 13kD, synthesized in all nucleated cells at a constant rate. It is present in an unglycosylated protein form and is ubiquitous in animal and plant tissue. It participate in proteolytic regulation between the interior and the exterior of the cell [7,12]. Due to its free filtration in the glomerulus with 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 attributed to kidney function but is also thought to be 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 leads to development of AF in patients with renal dysfunction, this does not explain the development of AF in earlier phases of renal dysfunction. In this situation, some researches make the beneficial attempt to these aspects [13,14]. Both the ARIC Study [13] and the Heart and Soul Study [14] only demonstrated the association between AF and renal function estimated by urinary albumin-to-creatinine ratio (ACR) and cystatin C-based glomerular filtration rate (eGFR_{cys}) rather than cystatin C itself. The Malmö Diet and Cancer study [9] only provide evidence that natriuretic peptides and CRP instead of cystatin C improve prediction of incident heart failure and AF in the general population in addition to conventional risk factors. However, these studies [9,13,14] on cystatin C and AF are not discussed at all.

One possible mechanism for a higher prevalence of AF in early stages of renal insufficiency could be explained by inflammation [15]. In this study, as an indicator, only cystatin C among biochemical indicators (such as creatinine and blood urea nitrogen) reflecting renal function in multivariate analysis had strong connection with AF. It is explained by the fact that cystatin C is more sensitive than other markers as a measure of renal function and is an inflammatory factor. Some researches 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, physical activity, diet and muscle mass, and ethnicity [9].

Many researchers have ascertained that cystatin C has a linear positive correlation with a variety of inflammatory cytokines such as hsCRP and reflects the severity of inflammatory activity, independent of renal function [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, this is followed by repair of the local tissue damage by fibrous tissue. As a result of this pathological process, atrial remodeling ensues [6–8]. It is worth mentioning that Targoński et al. found that the serum concentration of hsCRP is closely, positively correlated with the diameter size of left atrium [16]. The result of this study was consistent with Targoński's conclusion and showed that

the serum concentration of cystatin C also coincided with left atrial diameter.

This study confirmed that atrial fibrillation groups had higher values of cystatin C, hsCRP and left atrial diameter than those in the control group. Furthermore, persistent atrial fibrillation group had significantly higher values of cystatin C, hsCRP and left atrial diameter than those in paroxysmal AF and control groups. At the same time, correlation analysis showed that cystatin C is closely related to hsCRP and left atrial diameter of patients with atrial fibrillation. Therefore it follows that the inflammatory cytokines such as cystatin C and hsCRP should modulate process of inflammatory, participate in the hypertrophic degeneration of atrial muscle fiber, induce atrial structural abnormalities in patients with atrial fibrillation and thus lead to atrial electrical remodeling [6–8]. Inflammation is closely associated to atrial fibrillation [6] and may be the important medium which links atrial fibrillation with known risk factors (such as high blood pressure and obesity, etc.) responsible for the 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 has 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 that a rise the augment of hsCRP increased the risk of AF by 31% in the elderly [18]. In this study, monofactorial analysis showed 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 in the regression equation, 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 disease 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 which are also the components of metabolic syndrome. The risk of developing AF in patients with metabolic syndrome increased by 88%, compared to those without metabolic syndrome.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 body mass index, blood pressure, blood sugar and lipid levels [12]. Researches 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 connect cystatin C with metabolic syndrome [7,20]. Presumably, from another perspective, atrial fibrillation and the metabolic syndrome may have a common pathological relationship mediated by inflammatory biomarkers such as cystatin C. This study confirmed that body mass index, systolic blood pressure, fasting blood glucose and low-density lipoprotein cholesterol in AF groups, especially in permanent atrial fibrillation group (group AF2), were higher than those in the control group. Blood pressure is the most common risk factor of atrial fibrillation; moreover systolic blood pressure being the better predictor of atrial fibrillation than diastolic blood pressure [3]. This study also revealed that systolic blood pressure closely correlated to cystatin C as showed in the univariate analyse. Linssen, et al. pointed out that AF facilitate the progression of heart failure 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 heart failure [21]. As shown in this study, left ventricular ejection fraction 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 body mass index 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 group AF, 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 and 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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THE INFLUENCE OF EARLY LEFT VENTRICLE REMODELING OVER QTC CHANGES IN HIGHLY TRAINED PREADOLESCENT FOOTBALLERS

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Aim. To assess the correlation between left ventricle remodeling induced by physical training with QTc duration in preadolescent professional football players.

Material and methods. Ninety-four highly trained male footballers (mean aged 12,85±0,84) competing in the Serbian Football League (at least 7 training hours/week) and 47 age-matched healthy male controls were enrolled in the study. Main outcome measures: They were screened by ECG and echocardiography at a tertiary referral cardio center. The control group had sedentary life style (less than 2 training hours/week). QTc values and left ventricle dimensions were compared in these two groups.

Results. In all participants, normal values of QTc interval were registered. Mean QTc in athletes was significantly higher compared to non-athletes (419,89±13,07 msec vs 399,78±13,27 msec) ($p<0,001$). QTc interval had strong positive correlation to left atrium dilatation, LV dilatation, LV mass and LV mass index. There was no correlation between QTc interval and LV wall thickness, but there were correlations between QTc interval duration and specific LV mass indexes ($LVM/BSA^{1,5}$ and $LVM/h^{2,7}$).

Conclusion. QTc interval prolongation is present in early stage of athlete's heart remodeling, hence QTc prolongation could be the early ECG marker of physiological LV remodeling in young preadolescent footballers, without any other standard ECG and echocardiographic signs of early LV hypertrophy. This could be explained by a different pattern of left ventricle remodeling in preadolescent period, where LV wall thickness increase cannot usually be seen and the predominant characteristic is left ventricle dilatation.

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Key words: athletes, cardiology, echocardiography, electrocardiography, heart, footballers.

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QTc- QT corrected, LV — left ventricle, BSA- body surface area, ECG — electrocardiogram, LA — left atrium, AO — aortic root (AO), LVED — left ventricular end diastolic dimension, LVES — left ventricle end systolic dimension, PWd — left ventricle posterior wall diastolic dimension, IVSd — interventricular septal diastolic dimension, ASE — American Society of Echocardiography, LVM — left ventricular mass, LQTS — long QT syndrome, SD — standard deviation, h — height, LVH — left ventricular hypertrophy, QRS d — QRS duration, QRS v — QRS voltage, PR interval — duration of PR interval, P wave v — P wave voltage, HR — heart rate.

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ВЛИЯНИЕ РАННЕГО РЕМОДЕЛИРОВАНИЯ ЛЕВОГО ЖЕЛУДОЧКА ПРИ ИЗМЕНЕНИЯХ QTc У ВЫСОКОКВАЛИФИЦИРОВАННЫХ НЕПОЛОВОЗРЕЛЫХ ФУТБОЛИСТОВ

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Цель. Для оценки корреляции между ремоделированием левого желудочка, индуцированной физическими нагрузками, и продолжительностью QTc у неполовозрелых профессиональных футболистов.

Материал и методы. Девяносто четыре высококвалифицированных футболистов мужского пола (средний возраст 12,85±0,84), тренирующихся в Сербской Футбольной Лиге (по крайней мере, 7 учебных часов в неделю) и 47 подростков здоровых мужчин были включены в исследование. Основные критерии оценки: они были обследованы с помощью ЭКГ и ЭхоКГ в местном кардиологическом центре. Исследуемые в контрольной группе вели малоподвижный образ жизни (менее 2 учебных часа в неделю). Значения QTc и размеры левого желудочка сравнивались у этих двух групп.

Результаты. Нормальные значения интервала QTc были зарегистрированы у всех участников. Значения QTc у спортсменов были значительно выше, по сравнению с не-спортсменами (419,89±13,07 мс vs 399,78±13,27 мс) ($p<0,001$). Интервал QTc имел сильную положительную корреляцию к дилатации левого предсердия, дилатации ЛЖ, ЛЖ массы и индексу массы ЛЖ. Не было никакой корреляции между интервалом QTc и толщиной стенки ЛЖ, но имелась корреляция между интервалом QTc, длительностью и специфичностью индекса массы ЛЖ ($LVM/BSA^{1,5}$ and $LVM/h^{2,7}$).

Заключение. Удлинение интервала QTc присутствует в ранней стадии ремоделирования сердца спортсмена и, следовательно, удлинение QTc

может быть ранним ЭКГ-маркером физиологического ремоделирования ЛЖ у молодых неполовозрелых футболистов, без каких-либо других стандартных ЭКГ и эхокардиографических признаков ранней гипертрофии ЛЖ. Это может быть объяснено различной формой ремоделирования ЛЖ в половозрелый период, когда увеличение толщины стенки ЛЖ невозможно определить визуально и преобладающая характеристика является увеличением ЛЖ.

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Introduction

ECG and echocardiographic changes in athletes are common and usually reflect structural and electrical remodeling of the heart as an adaptation to regular physical training and hemodynamic changes that alter the loading conditions of the heart, causing the athlete's heart syndrome. [1] However, the level and duration of training or competition, aerobic capacity and type of sports activity play an important role in the extent of physiological changes of athlete's heart syndrome. Several studies have shown that corrected QT interval (QTc) interval in rest, although still in physiological limits, is prolonged in adult professional athletes compared to sedentary age-matched controls, [2] The main cause of this prolongation was physiological left ventricular hypertrophy, common in athletes. Left ventricular hypertrophy is related to the level and duration of physical training and is less common in adolescent athletes, where the left ventricular dilatation is frequently seen. [3] However, some new studies proved that left ventricular dilatation is the main pattern of the early left ventricle remodeling in the beginning of the active sports career in the youngest athletes. [4, 5] The 2005 Study Group of Sport Cardiology of the European Society of Cardiology recommend that a 12-lead ECG (in addition to a history and physical examination) should be a part of the pre-participation screening of young competitive athletes for prevention of sudden death. That document included criteria for a positive 12-lead ECG and specified values of the heart rate corrected QT interval (QTc more than 440 ms in males and 460 ms in females) [6].

In the following study the hypothesis was tested: there might be a difference in QTc interval duration between two compared groups in early adolescent period: elite football players and age-matched sedentary controls, and that QTc interval, measured from a single lead, would correlate with echocardiographic parameters of professional football players. The second aim of this study is to address the relative lack of data in the literature regarding normal values of QTc in adolescent population of football players and to define normal ranges of QTc for the athletes in early adolescent period.

Material and Methods

Study design

A group of 94 Caucasian elite male footballers aged 12,85 (0,84), all members of the National Football Premier League clubs age range 12–14 years. The control group consisted of 47 healthy male age-matched sedentary controls, who were not exercising regularly (sport-training for not more than 2 hours a week). None of the participants had any symptoms attributable to cardiovascular disease. No subject was taking any form of prescribed drug treatment. Physical examination was without any pathological findings in all participants. They all were normotensive and nonsmokers. All athletes had been

regularly engaged in active training for at least three years and were in their active training season. They had, on average, 9 hours of weekly training which included: 5 hours specific football training, 2 hours anaerobic dynamic training, 1 hour strength training and 1 hour aerobic endurance activities. The sample size was calculated to have a power more than 80% to detect a difference at $p < 0,05$. [7]

Echocardiographic evaluation was performed by the same experienced cardiologist who was blind to the subject's training group, on every occasion using Acuson Sequoia computed sonography platform with a probe frequency 3.5 MHz vector array format transducer following the recommendations of the American Society of Echocardiography. [7] The images were obtained in the parasternal long and short axis, in left lateral position and also in the four chamber view and then analyzed off-line. Both M-Mode and cross sectional studies were performed. The measurements of the left atrium (LA), aortic root (AO), left ventricular end diastolic dimension (LVED), left ventricle end systolic dimension (LVES), left ventricle posterior wall diastolic dimension (PWd), interventricular septal diastolic dimension (IVSd), were done in the parasternal long axis view, by the average of 3 consecutive cardiac cycles with concomitant ECG and the average was calculated. Left ventricular ejection fraction (EF) was calculated by Simpson's rule. Left ventricular mass (LV mass) was calculated using the method described by Devereux et al. [7]

$$LVM = 1,04 \times [(LVED + PWd + IVSd)^3 - LVED^3] - 13,6g$$

Left ventricular mass index (LVMI) was calculated by standard dividing LV mass by BSA. [7]

All heart valves were assessed by standard technique in order to exclude significant valvular and subvalvular obstruction and regurgitation. Valve regurgitation severity was evaluated according to the recommendations of the American Society of Echocardiography (ASE) Guidelines [7].

As LVM is known to vary with body size and composition, normalization of LV dimensions according to body size is very important in comparisons between different subjects groups. In children and adolescents increased cardiac size is directly proportional to the increases of body height, so these adjustments according to body size were done for comparison of cardiac dimensions: LV mass findings were adjusted to $BSA^{1.5}$ and LVM was additionally adjusted to $height^{2.7}$ [7].

Standard 12-lead electrocardiogram (EGC) was recorded using a Nihon Cohden recorder with a paper speed of 25 mm/s and amplification of 0.1 mV/mm. The QT interval was measured in all leads from the onset of QRS complex to the end of T wave, defined as the intersection of isoelectric line and the tangent of the maximal downward limb of the T wave. [15] The U-wave was excluded during the measurement of the QT interval, except when the T wave was biphasic or in the presence of T–U complexes

where the identification of the termination of the T wave was difficult. In such cases, the U-wave was included if it exceeded 50% of the T-wave amplitude. In the presence of biphasic T waves, we have also assessed the QT interval in other leads that did not exhibit biphasic T waves. The lead with the longest QT interval was used to obtain an average QT over three to five consecutive beats. The QTc values were derived using Bazett's formula, which has been most widely used in all large studies evaluating patients with LQTS [16]. The Bazett correction is commonly used in QTc interval investigations and involves dividing the uncorrected QT (in seconds) by the square root of the RR interval (in seconds). The limitations of this method are over-correction at faster heart rates (lower RR intervals) and under-correction at slower heart rates (higher RR intervals).

All ECGs were analyzed independently by two independent cardiologists with a clinical and academic interest in LQTS, blinded to all clinical details of the subjects, using a millimeter ruler and calipers. According to internationally accepted guidelines, males with a QTc value of 440 ms and females with a QTc value of 460 ms were considered to have an abnormally prolonged QTc interval. [8]

Statistical analysis

Continuous data are expressed as mean (SD), with 5th and 95th percentile ranges to facilitate comparison with the data belonging to the controls. Statistical analysis was carried out using unpaired t-tests between groups. Statistical significance is stated as $p < 0.05$.

Results

Selected physical characteristics of the footballers and the controls are shown in Table 1.

The footballers had similar height as the control group, but significantly smaller weight and BSA. Heart rate was

Table 1

The characteristics of the 94 footballers and 47 age-matched non-athletes (the mean and SD)

	Footballers	Non-athletes
Age (years)	12,85 (0,84)	12,85 (0,86)
Height (cm)	159,36 (10,65)	162,71 (13,09)
Weight (kg)	48,27 (10,62) *	58,28 (13,07)
BSA (m ²)	1,45 (0,20) *	1,61 (0,24)
BMI (kg/M ²)	18,75 (1,92) *	21,59 (1,86)
HR (bpm)	83,49 (14,50) *	88,8 (5,19)
Systolic blood pressure (mmHg)	109,95 (8,08)	108,19 (6,71)
Diastolic blood pressure (mmHg)	65,74 (7,89) *	60,75 (5,80)

* — $p < 0,001$.

Abbreviations: BSA — body surface area, HR — heart rate.

significantly lower in athletes than in control subjects. Values of systolic blood pressure were similar in both groups, but diastolic blood pressure was higher in athletes, nevertheless normal.

Table 2 shows the mean, SD, and 5th to 95th percentile ranges of the echocardiographic measurements and QTc values of the footballers as well as of the controls.

There was no difference in LV wall thickness and LV mass in these two compared groups. LVMI was significantly bigger in adolescent footballers, as well as specific indexes of left ventricle in athletes, like $LVM/BSA^{1.5}$ ($p < 0,001$) and $LVM/h^{2.7}$ ($p < 0,0001$). Left atrial chamber size ($p < 0,001$), aortic root diameter ($p < 0,001$), LV end diastolic dimension ($p < 0,05$) and LV end systolic dimension ($p < 0,001$) were also significantly increased in the footballers compared to the age matched control group data. There also was no significant difference in mean left ventricular ejection fraction (EF) and shortening fraction (SF) in the compared groups. The footballers had mean (SD) ejection fraction 68,23 (4,36)% and the subjects in

Table 2

Comparison of the resting echocardiographic findings in 94 footballers and 47 age-matched non-athletes and correlation between QTc interval duration and echocardiographic parameters in adolescent young footballers (the mean and SD)

	Footballers	Non-athletes	QTc correlation
Ao (mm per $BSA^{0.5}$)	21,87 (2,08) *	15,65 (1,36)	0,478§
LA (mm per $BSA^{0.5}$)	23,18 (2,07) *	20,15 (2,87)	0,221§
LVED (mm per $BSA^{0.5}$)	38,72 (2,53) *	35,68 (2,54)	0,351§
LVES (mm per $BSA^{0.5}$)	25,83 (2,58) *	20,75 (2,30)	0,374§
IVSd (mm per $BSA^{0.5}$)	7,08 (0,70)	6,53 (0,81)	0,089
PWd (mm per $BSA^{0.5}$)	6,82 (0,73)	6,46 (0,80)	-0,045
LVM (g)	160,14 (33,14)	149,59 (34,01)	0,096
LVMI (g per BSA)	109,79 (15,04) *	92,84 (18,29)	0,235§
$LVM/BSA^{1.5}$ (g per $BSA^{1.5}$)	91,55 (13,86) *	73,73 (16,54)	0,339§
$LVM/h^{2.7}$ (g per $h^{2.7}$)	45,78 (9,47) *	40,65 (9,29)	0,298§
QTc (msec)	419,89 (13,27) *	399,78 (13,07)	/

* — $p < 0,01$ compared to controls, § — $p < 0,01$ correlation of echocardiographic parameters and QTc interval duration.

Abbreviations: Ao — aortic root diameter, LA — left atrium, LVED — left ventricular end-diastolic dimension, LVES — left ventricular end-systolic dimension, IVSd — ventricular septal thickness (diastole), PWd — ventricular posterior wall thickness (diastole), LVM — left ventricular mass, LVMI — left ventricle mass index, h — height.

Table 3**The ECG characteristics of the 94 footballers and 47 age-matched non-athletes (the mean and SD)**

	Footballers	Non-athletes
QRS d (msec)	82,44 (1,30) *	76,01 (0,71)
QRS v (mV)	159,36 (10,65) *	162,71 (13,09)
PR interval (msec)	174,02 (3,57) *	162,84 (1,56)
P v (mV)	1,96 (0,16) *	1,34 (0,46)

* — $p < 0,001$.**Abbreviations:** QRS d — QRS duration, QRS v — QRS voltage, PR interval — duration of PR interval, P wave v — P wave voltage.

the control group 68,49 (4,72)%. The mean (SD) fraction of shortening was 38,01 (3,84)% in footballers and 38,36 (3,95)% in the control group. No regional wall motion abnormalities of either the right or the left ventricle were seen. All study participants had normal LV diastolic function and E/a ratio >1 .

All participants (aged 12–14) had normal values of QTc interval. Mean QTc interval in athletes in rest was significantly longer $419,89 \pm 13,07$ msec, compared to mean QTc in the control sedentary group — $399,78 \pm 13,27$ msec ($p < 0,001$). The mean and SD of the QTc values in footballers as well as in non-athletes are shown in Table 2, together with correlation of these parameters to echocardiographic measurements.

In Table 2, the mean and SD of the QTc values in footballers as well as in non-athletes together with correlation of these parameters to echocardiographic measurements.

QTc interval duration in athletes had not very strong, but indeed positive correlation to left atrium dilatation, LV dilatation, LVMI, and most important to $LVM / BSA^{1.5}$ and $LVM / h^{2.7}$ indexes. There was no correlation between QTc interval duration and LV wall thickness.

In Table 3 ECG characteristics of footballers and non-athletes were compared.

Discussion

The study is unique regarding age of the investigated population widely and the first of the kind in Serbia. The data indicate normal values of QTc interval in all participants; however, QTc intervals in athletes were highly significantly longer. Positive correlations between QTc interval duration and echocardiographic dimensions of the left heart's cavities (ventricle and atrial) and aortic root were proven, suggesting the concomitant morphological, functional and electrical early heart remodeling even in the preadolescent period. It was not surprising that the resting heart rates of the athletes were faster than the typically reported heart rate in the previous studies, since this was the unique age group of athletes.

There was no difference in LV wall thickness and LV mass in these two compared groups. However, we could not exactly say there was no LV hypertrophy, since LVMI

was significantly bigger in adolescent footballers, as well as specific indexes of left ventricle in athletes, like $LVM / BSA^{1.5}$ ($p < 0,001$) and $LVM / h^{2.7}$ ($p < 0,0001$). It is very important to observe that, although there are no increased dimensions of the LV wall, QTc prolongation in preadolescent footballers is very closely linked to the LV hypertrophy, characterized by increased LVMI and specific LV indexes ($LVM / BSA^{1.5}$ and $LVM / h^{2.7}$).

As it is well known, the long QT syndrome (LQTS) is a genetic disorder characterized by prolongation of the QT interval in the electrocardiogram (ECG) and a propensity to torsades de pointes ventricular tachycardia frequently leading to syncope, cardiac arrest, or sudden death usually in young otherwise healthy individuals. [9] The first description of QT interval in athletes during rest and exercise was given by Ring GC et al. in 1972. [9] In athlete population the QTc interval prolongation was demonstrated through a huge number of studies; in all of them there were also left ventricular hypertrophy with increased left ventricle wall thickness, suspected to be the cause of the prolongation. But increased left ventricle wall thickness is not common in preadolescent period and consequently QTc prolongation is less likely to be expected.

The relationship between occurrence of arrhythmias and QT prolongation in athletes was described later [10], some studies have even linked QT interval prolongation in physical exercise to some undiagnosed cardiac disease [11]. The QT interval prolongation was proved even in animals with high physical exercise — highly trained dogs [11].

The prevalence of QT interval prolongation in asymptomatic elite athletes was recently reported as 0,4%, or 1 in 286 patients. Palatini et al. reported in a group of 30 young athletes the QTc interval prolongation, but no correlations between QTc prolongation and the degree of severity of ventricular ectopic beats, heart rate or echocardiographic dimensional and functional findings were found [12]. Factors which play a role in these QT interval changes are a lower intrinsic heart rate, an increased parasympathetic or vagal tone, a decrease in sympathetic tone, structural cardiac adaptations, and non-homogeneous depolarization of the ventricles. Alterations are mostly seen in athletes engaged in high intensity dynamic endurance sports. It is important to recognize that several of the ECG changes that can accompany athletic conditioning resemble pathological ECG features and may mimic structural heart disease. QTc interval prolongation was described by Stolt et al. in female athletes, much older than our group [13]. In the same study, QTc prolongation also correlated with LV and RV mass and increased LV wall thickness. According to Sharma et al. highly significantly prolonged QTc interval should be linked to the frequently registered ECG signs of left ventricle hypertrophy [14].

However, still our data indicate no correlation between QTc interval duration and LV wall thickness, analysis of

specific LV mass indexes revealed significant differences within, suggesting that correlation between these indexes and QTc prolongation could be the explanation for the QTc prolongation. Furthermore, QTc prolongation could be the early ECG marker of physiological LV remodeling in young preadolescent footballers, without any other standard ECG and echocardiographic signs of early LV hypertrophy. This fact could be explained by a different pattern of left ventricle remodeling in preadolescent period, where LV wall thickness increase cannot usually be seen and the predominant characteristic is left ventricle dilatation. In our opinion QTc prolongation in athletes is related to the early cardiac remodeling and can be seen even after a short period of training; nevertheless recommended normal values of QTc interval in young preadolescent footballers should be expected [15].

Limitations

The study is limited to Serbian Caucasian preadolescent footballers and differences with other races can occur. However, the number of investigated elite footballers in the preadolescent age is limited by the small number of the elite footballers of that age — all preadolescent elite footballers were enrolled in our study. Although further studies are necessary, we expect athletes with different

sports to have similar findings. Both the development and degree of LVH and QTc prolongation are multifactorial, thus hypertrophy modulated by other causes (i.e. genotype) could not be excluded. Although Bazett's correction that was used may overcorrect more at a heart rate of 89 than at 83, in our opinion this will not likely make a difference in the results of the study.

Conclusion

In summary, the study showed that there is a prolongation of QTc interval in highly trained preadolescent footballers compared to the QTc interval in teenagers with sedentary life style, correlating with specific LV mass indexes. However, this prolongation is still within recommended values. QTc prolongation could be the early ECG marker of physiological LV remodeling in young preadolescent footballers, without any other standard ECG and echocardiographic signs of early LV hypertrophy.

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IMPACT OF ECHOCARDIOGRAPHIC OPTIMIZATION OF RESYNCHRONIZATION PACE-MAKER USING DIFFERENT PACING MODALITIES AND ATRIOVENTRICULAR DELAYS ON ACUTE HEMODYNAMIC RESPONSE AND LONG TERM PROGNOSIS

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Cardiac resynchronization therapy (CRT) improves ventricular dyssynchrony and is associated with an improvement in life quality and prognosis.

Aim. The aim of study was to examine acute hemodynamic changes with different of CRT device modalities throughout optimization procedure and its impact on one year prognosis.

Material and methods. The study comprised 62 patients with severe left ventricular systolic dysfunction (LVEF $24.6 \pm 4.4\%$, QRS duration 154.71 ± 14.92 ms, NYHA class III/IV 47/15) with implanted CRT device. After implantation and before discharge all the patients underwent optimization procedure guided by Doppler echocardiography. Left (LVPEI) and right (RVPEI) ventricular pre-ejection intervals, interventricular mechanical delay (IVD) and the maximal rate of ventricular pressure rise during early systole (max dP/dt) were measured during left and biventricular pacing with three different atrioventricular (AV) delays. Stroke volume derived from the left ventricular outflow tract velocity–time integral (VTI) of left ventricular outflow tract (LVOT VTI) was measured as well. After one year patients underwent clinical, echocardiographical examination and 6 minute walking test.

Results. After CRT device optimization, optimal AV delay and CRT mode were defined. Left ventricular pre-ejection intervals changed from 175.4 ± 21.5 to 142.6 ± 16.7 ($p < 0.01$), RVPEI from 108.6 ± 18.9 to 127.3 ± 18.3 ($p < 0.001$), IVD from 71.3 ± 14.8 to 24.7 ± 7.6 ($p < 0.001$) and dP/dt from 532.2 ± 74 to 675.2 ± 111 ($p < 0.001$). Left ventricular outflow tract VTI increased after optimization procedure from 18 ± 3.4 to 21 ± 1.5 cm ($p < 0.05$).

Conclusions. Echocardiographic optimization procedure emphasizes the individualized approach in CRT optimization procedure in order to derive the best short and long term results.

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Key words: CRT, echocardiographic optimization, heart failure, prognosis, life quality.

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CRT — cardiac resynchronization therapy, CRT-P — cardiac resynchronization therapy pacemaker, CRT-D — cardiac resynchronization therapy pacemaker with an ICD, 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, HF — heart failure, ICD — Implantable cardioverter defibrillator, IVD — inter-ventricular conduction delay, LV — left ventricle, LVEF — left ventricle ejection fraction, LVPEI — pre-ejection interval of the left and ventricle, max dP/dt — maximal rate of ventricular pressure rise during early systole, NYHA — New York Heart Association, PEP LV — pre-ejection interval of left ventricle, PEP RV — pre ejection interval of right ventricle, RV — right ventricle, RVPEI — pre-ejection interval of the left and right ventricle, Six (6) MWD — six minute walking distance, SPWMD — septal-posterior wall motion delay, LVOT VTI — left ventricular outflow tract, VTI — velocity–time integral, VT — ventricular tachycardia, VF — ventricular fibrillation, QoL — quality of life.

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ВЛИЯНИЕ ЭХОКАРДИОГРАФИЧЕСКИХ ОПТИМИЗАЦИИ РЕСИНХРОНИЗИРУЮЩЕЙ ТЕРАПИИ ПАСЕ-МАКЕР, С ИСПОЛЬЗОВАНИЕМ РАЗЛИЧНЫХ МЕТОДОВ СТИМУЛЯЦИИ И АТРИОВЕНТРИКУЛЯРНОЙ ЗАДЕРЖКИ НА ГЕМОДИНАМИЧЕСКИМИ ОТВЕТ И ДОЛГОСРОЧНЫЙ ПРОГНОЗ

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Сердечная ресинхронизирующая терапия (СРТ) улучшает желудочковую диссинхронию и связана с улучшением качества жизни и прогноза заболевания.

Цель. Целью исследования явилось изучение гемодинамических изменений с разными устройствами СРТ, методов оптимизации всей процедуры и ее влияние на один год прогноза.

Материал и методы. В исследование вошли 62 больных с тяжелой систолической дисфункцией левого желудочка (LVEF $24.6 \pm 4.4\%$, длительность комплекса QRS 154.71 ± 14.92 ms, класс NYHA III/IV 47/15) с имплантированными ЭЛТ-устройствами. После имплантации и перед выпиской всем пациентам была проведена процедура оптимизации под контролем доплер-эхокардиографии. Левый (LVPEI) и правый (RVPEI) желудочковый pre-ejection интервалы, межжелудочковая механическая задержка (IVD) и максимальное значение повышения давления в желудочке во время ранней систолы (max dP/dt) были измерены во время лево- и бивентрикулярной электрокардиостимуляции с тремя различными атриовентрикулярными (AB) задержками. Были измерены ударный объем производный от пути оттока левого желудочка, как и скорость-временной интеграл (VTI) пути оттока левого желудочка (LVOT VTI). После одного года пациенты прошли клиническое, эхокардиографическое исследование и тест 6 минутной ходьбы.

Результаты. После оптимизации СРТ-устройства, оптимальная АВ задержка и режим СРТ были определены. Pre-ejection интервалы левого желудочка изменились от 175.4 ± 21.5 до 142.6 ± 16.7 ($p < 0.01$), RVPEI от 108.6 ± 18.9 до 127.3 ± 18.3 ($p < 0.001$), IVD от 71.3 ± 14.8 до 24.7 ± 7.6 ($p < 0.001$) и dP/dt от 532.2 ± 74 до 675.2 ± 111 ($p < 0.001$). VTI пути оттока левого желудочка возросло после процедуры оптимизации с 18 ± 3.4 до 21 ± 1.5 см ($p < 0.05$).

Заключение. Эхокардиографическая процедура оптимизации подчеркивает индивидуальный подход в оптимизации процедуры СРТ в целях определения лучших краткосрочных и долгосрочных результатов.

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Ключевые слова: СРТ, эхокардиографическая оптимизация, сердечная недостаточность, прогноз, качество жизни.

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Introduction

In patients with moderate to severe symptoms of heart failure (HF) and bundle branch block with prolonged duration of QRS complex, cardiac resynchronization therapy (CRT) with or without an implantable cardioverter-defibrillator reduces HF hospitalizations and prolongs survival compared with an optimal medical therapy alone. Moreover, CRT with its dyssynchrony reduction improves symptoms and quality of life (QoL), increases exercise tolerance, and reduces left ventricular dilatation [1–4]. However in a significant number of patients this therapy does not improve symptoms and signs of the disease [5, 6]. The causes of the inadequate response could be the absence of dyssynchrony even if the QRS complex duration is prolonged, inadequate positioning of the electrode or suboptimal parameters of the resynchronization pacemaker [7, 8].

The studies have shown that the basal mechanic dyssynchrony could have the predictive role regarding the hemodynamic response to CRT [9]. In CARE-HF study in the selection of patients for CRT beside recommended parameters for dyssynchrony measurement they have used parameters of the conventional Doppler echocardiography: prolonged pre-ejection interval of the left ventricle (LVPEI >140 ms) and increased difference between pre-ejection intervals of the left and right ventricles (IVD >40 ms) [10].

In the adequately selected patients it has been proved that the acute obtained required hemodynamic changes could persist during the 6-month follow up period [11]. Adlbrecht et al. in the retrospective analysis showed that echocardiographic optimization of the atrio-ventricular (AV) -interval in patients with CRT was independently associated with improved clinical outcome during 32 months of median follow up [12]. Accordingly, the acute hemodynamic response to CRT measured by the percentage of the change in the value of the basal maximal slope of ventricular pressure increase during the early systole (dP/dt) is associated with the improved clinical parameters independently of the cardiomyopathy aetiology [13]. Beside the advantages of the tissue Doppler in the evaluation of the candidates for this therapy, a conventional Doppler echocardiography is considered as a useful tool not only in the baseline assessment of the patients but also in the individual approach to the non-invasive assessment of the most effective pacing modalities and AV delays [14, 15].

The primary goal of this study was the assessment of the changes in the basal echocardiographic parameters: dP/dt, pre-ejection interval of the left and right ventricle (LVPEI, RVPEI) and their difference (IVD) in optimisation of the resynchronization pacemaker by using the different modalities of the pacing and the atrioventricular delay. Stroke volume derived from the left ventricular outflow tract velocity–time integral (VTI) of left ventricular outflow tract (LVOT VTI) was measured as well. One year after the

device implantation we determined mortality rate, number of re-hospitalizations due to worsening of HF, six minute walking distance (6MWD), functional New York Heart Association (NYHA) class and the end-diastolic diameter of the left ventricle (EDD).

Methods

We enrolled 62 patients with chronic systolic heart failure (left ventricle ejection fraction — LVEF <35%) in our study. They were in NYHA class III–IV, with left bundle branch block (QRS duration >130 ms) and mitral regurgitation which enabled the measurement of the dP/dt.

Before the implantation of the resynchronization pacemaker, patients underwent the coronary angiography in order to determine the aetiology of heart failure.

Atrio bi-ventricular pacemaker with implantable cardioverter defibrillator was implanted in 18 patients, while the others got the atrio-ventricular device. The resynchronization pacemaker was implanted trans-venal with the left ventricle electrode placed in the anatomically adequate coronary sinus branch with the acceptable threshold pacing and without diaphragm stimulation. The right ventricle electrode was positioned in the apicoseptal region of the right ventricle.

During the first three days, before the hospital discharge, we did the optimisation of the resynchronization pacemaker using the echocardiography Doppler technique. Echocardiographic apparatus General Electric Medical SystemsTM Vivid 4 with a sonde of 2.5 MHz was used. By using the pulse Doppler speed of 100 mm/s we analysed the aortic and pulmonary flow. We obtained three values of each parameter and the mean value was taken for the analysis. The pre-ejection interval of the left ventricle (LVPEI) was assessed by the transaortic Doppler flow measurement from the beginning of the QRS complex and transaortic ejection signal. The pre-ejection interval of the right ventricle (RVPEI) was measured from the beginning of the QRS complex to the beginning of the transpulmonary ejection signal. The difference between the LVPEI and RVPEI was determined as an inter-ventricular delay (IVD). The positive value of the IVD was an indicator of the delayed left ventricle ejection, while the negative value of this parameter was considered as an indicator of the delayed ejection of the right ventricle.

Using the continuous Doppler we assessed the mitral flow and by measuring the slope of the mitral regurgitation signal acceleration we determined the dP/dt (16). We tested three values of the AV delay: long 150 ms, intermediate 120 ms and short 90 ms. Intermediate AV delay (120 ms after sensed atrial event) with bi-ventricular pacing was in accordance with the standardized parameters of the CRT device.

As the optimal CRT configuration were considered bi-ventricular or left ventricle pacing and AV delay with the best echocardiographic parameters for each patient.

Continuous variables were presented as a mean value $\pm 1SD$, and the ordinary as a frequencies. Student's T test was used for comparison of the basal values during the standard and optimal CRT mode. We correlated interdependence between the measured parameters (Pearson's and Spearman's correlation coefficients were used). Chi-square test was used for the comparison of the frequency distribution between basal and NYHA class and one year after implantation of the CRT. $P < 0.05$ was considered statistically significant. SPSS 17 for Windows package was used for the analysis.

The study complied with the Declaration of Helsinki and it was conducted in the Clinic for the cardiovascular diseases, Clinical Centre Nis. The Medical Ethical Committee of the Medical Faculty of the University of Nis, Serbia, approved the study protocol. All participants submitted written informed consent.

Results

Demographic data are presented in the Table 1. We included in the study patients with significant left ventricle dysfunction ($EF = 24,60 \pm 4,4\%$) with manifested heart failure: NYHA III (47, 75,8% of patients) and NYHA IV (15, 24,2% of patients) functional class, Ischemic aetiology was found in 19,4% of patients, non-ischemic in 69,4% of patients and non-compacted cardiomyopathy had 11,2% of patients,

Distribution of the optimal mode of the CRT device is presented in Table 2. The majority of patients (57) had the optimal biventricular pacing. In five patients beside the improvement achieved with the biventricular pacing we found optimal left ventricle pacing. The standardized AV delay of 120 ms was optimal in 25 (40,3%) patients, shortened AV delay of 90 ms was found in 29 (46,7%) patients and increased AV delay of 150 ms was optimal in 8 (13%) patients.

All the measurements were obtained without resynchronization and during the left and biventricular pacing. Basal values and the one obtained after optimization of the LVPEI, RVPEI, IVD, dP/dt , VTI are shown in the Table 3. All the indices of the left ventricle hemodynamic were significantly improved particularly after the CRT

Table 1

Baseline patients' characteristics

age (years $\pm$ SD)	61,06 $\pm$ 10,00
men / women n (%)	46 (74,2) / 16 (25,8)
non-ischemic cardiomyopathy n (%)	43 (69,4)
ischemic cardiomyopathy n (%)	12 (19,4)
non-compact cardiomyopathy n (%)	7 (11,2)
QRS (ms), ($\pm$ SD)	154,71 $\pm$ 14,9
EF (%) $\pm$ SD	24,60 $\pm$ 4,4
NYHA III/IV [n (%)]	47 (75,8) / 15 (24,2)

Table 2

Distribution of atrioventricular delay (AV) and optimal cardiac resynchronization therapy (CRT) modality

Pacemaker characteristics	Number of patients (n = 62)	
	n	%
biventricular pacing	57	91,9
left ventricle pacing	5	8,1
prolonged AV delay	8	13
intermediate AV delay	25	40,3
short AV delay	29	46,7

device optimization. Pre-ejection interval of the left ventricle and dP/dt were significantly reduced, while, RVPEI, VTI and IVD were significantly increased.

The measured parameters with standardized and optimal AV delays are presented in the Table 3.

We correlated QRS complex duration with echocardiographic parameters in basal conditions and with standardized and optimal CRT device conditions. We found significant correlation between QRS duration with the standardized IVD ($p < 0.05$) which indicates that the wide QRS complex is the predictor of the decreased interventricular delay after CRT device implantation.

After one year follow up period we found significant reduction in the end-diastolic diameter of the left ventricle (from 71,9 $\pm$ 7,5 mm to 67,4 $\pm$ 6,8 mm, $p < 0,001$) with significant improvement in NYHA functional class (NYHA II — 44 patients (74,6%), NYHA III — 13 (22,03%) and NYHA IV- 2 patients (3,4%)) (Table 4).

Table 3

Variability of Doppler parameters ($r \pm SD$)

Parameter	Baseline value	Secondary conditions	Optimal conditions	Difference baseline vs. Optimal conditions (%)
LVPEI (ms)	175,4 $\pm$ 21,5	147,4 $\pm$ 16,7*	142,5 $\pm$ 13,78**	32,9 (18,7)
RVPEI (ms)	108,6 $\pm$ 18,9	124,9 $\pm$ 18,7**	127,3 $\pm$ 18,3**	18,7 (17,2)
IVD (ms)	71,3 $\pm$ 14,8	31,6 $\pm$ 6,7**	24,7 $\pm$ 7,6**	46,6 (65,3)
dP/dt	532,2 $\pm$ 74	622,5 $\pm$ 82,9**	675,0 $\pm$ 111**	143 (27)
VTI (cm)	18 $\pm$ 3,4	20 $\pm$ 1,0*	21 $\pm$ 1,5*	0,3 (16,6)

* $p < 0,001$ between basal and standardized, basal and optimal, optimal and standardized values; ** $p < 0,01$ between standardized and optimal values.

Abbreviations: LVPEI — pre-ejection interval of left ventricle, RVPEI — pre-ejection interval of right ventricle, IVD — difference between LVPEI and RVPEI, dP/dt — change of basal maximal slope of increase in ventricular pressure during the early systole (dP/dt) obtained from the mitral regurgitation signal.

Table 4

Changes of EDD of left ventricle and NYHA functional class after 1-year follow-up

Parameter	Basal conditions	1-year control values	p
EDD (mm), ($r \pm SD$)	71,92 $\pm$ 7,4	67,35 $\pm$ 6,8	< 0,001
NYHA II [n (%)]	0 (0)	44 (74.6)	< 0,001
NYHA III [n (%)]	47 (75.8)	13 (22.03)	< 0,001
NYHA IV [n (%)]	15 (24,2)	2 (3,4)	< 0,001

Abbreviations: EDD- end diastolic diameter, NYHA- New York Heart Association.

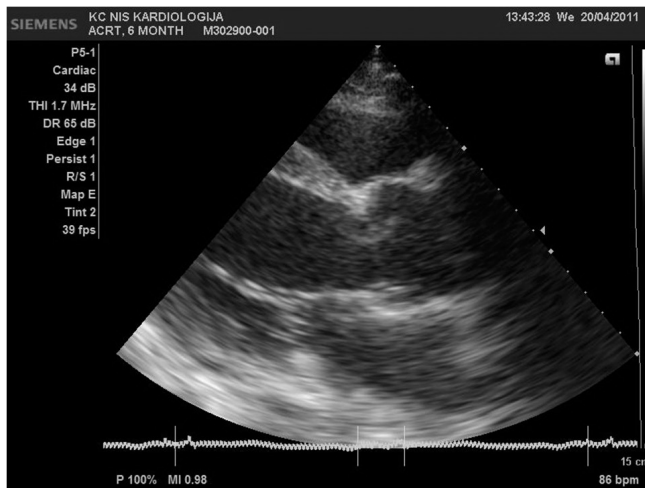


Fig. 1. Left and right ventricle before CRT implantation.

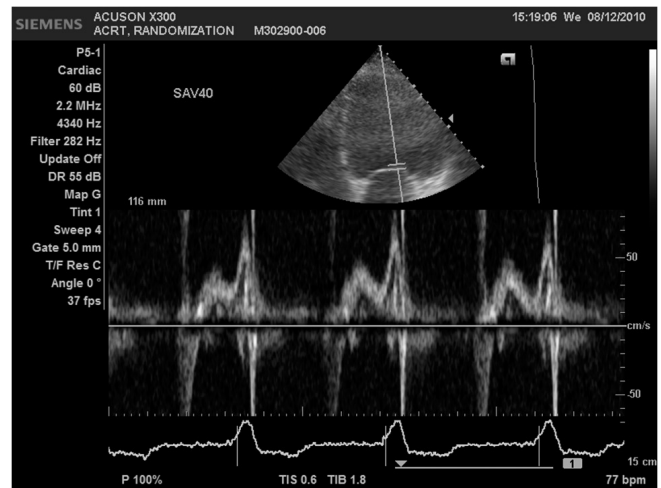


Fig. 3. Echocardiographic presentation of A-V optimization.

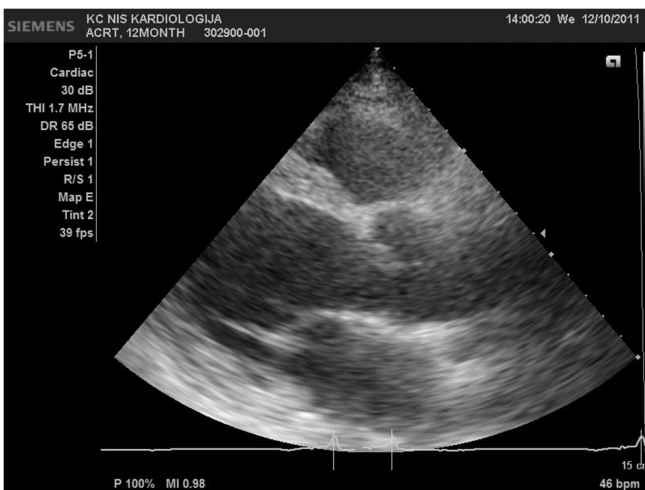


Fig. 2. Left and right ventricle 1 year after CRT implantation.

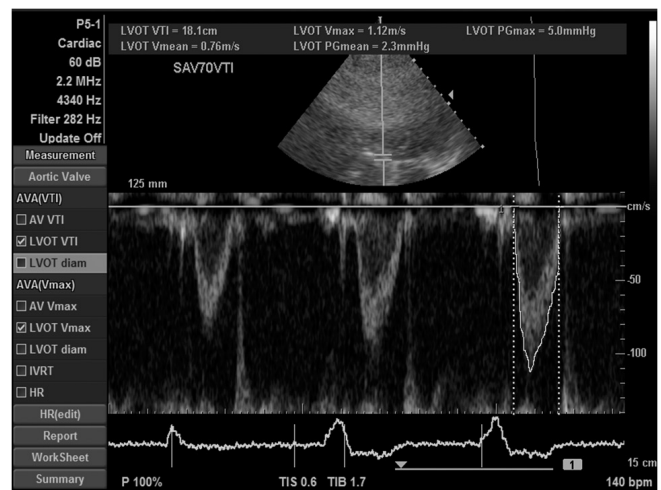


Fig. 4. Echocardiographic presentation of V-V optimization.

Echocardiographic presentations of left and right ventricle before CRT implantation and one year later are shown in Figure 1 and 2.

Three patients died during follow up period. The majority of patients was not re-hospitalized during one year of follow up (67,7%), while 22,6% had one hospitalization, 6,5% had two hospitalizations and 3,2% three hospitalizations due to worsening heart failure. We measured 6MWD at hospital discharge and after one year of follow up, 6MWD at baseline 222,32 $\pm$ 40,35 increased to 302,38 $\pm$ 74,8m, $p < 0,001$.

Discussion

Varieties of methods are used clinically for programming the AV delay, with no current consensus as to best practice. Many implanters use empirically program devices to a fixed AV delay interval and optimize only those patients who fail to respond to therapy [17]. Kamdare et al. showed that echocardiography was superior to an algorithm in St Jude medical CRT devices (QuickOpt™) which optimizes device automatically [18].

The most important finding of our study is that easy to obtain and low cost echocardiographic parameters such as pre-ejection intervals of the left and right ventricle (LVPEI, RVPEI) and their difference (IVD) as well as dP/dt , could be very useful in the setting of the optimal mode of resynchronization pacemaker. These lead to short and long term benefits for our patients — decreased LV volumes, improved QoL assessed as a better physical capacity (lower NYHA class and increased 6MWD).

The pre-ejection interval represents the electro-mechanic delay and isovolumetric time and it is in inverse correlation with the dP/dt [19]. In the preliminary MIRACLE study report, LVPEI is defined as a predictor of the CRT treatment efficiency [20, 21]. The interventricular delay is identified as a discordance of the left and right ventricle contractions and it is sought to be the predictor of the CRT treatment efficiency which was used in patients selection in CARE-HF study [3, 22, 23].

In our study we registered the change in values of LVPEI, RVPEI and IVD during the setting of the CRT device which shows that those parameters could be useful in selection of patients for this therapy and in process of the individual setting of these pacemaker parameters.

Ventricular contractility measured as a percentage of the change in the basal maximal slope increase of the ventricular pressure (dP/dt) is a prognostic predictor in patients with heart failure [24]. The change in dP/dt after CRT implantation is the measure of the overall influence of this device on cardiac function [14].

Adamson et al. have showed that the increase of dP/dt is significantly different in patients who have benefit from CRT from those who do not [22]. The invasive determination of dP/dt and pulse pressure in the process of CRT optimization is complicated, unrepeatable and time consuming method [25].

We found significant increase of dP/dt after CRT implantation ($p < 0,001$). Additional increase ($p < 0,01$) of this parameter is registered during the process of the CRT optimization.

Number of patients with moderate to severe mitral regurgitation before device implantation was 50 (80%). After CRT pacemaker implantation that number significantly decreased to 4 (6,7%), $p < 0,01$. By influencing on the severity of mitral regurgitation, CRT shows that the increase of dP/dt is the cause but not the consequence of the mitral regurgitation decrease [9, 26, 27]. The effect of the resynchronization therapy on the decrease of mitral regurgitation severity could be direct or late response to the synchrony achievement [28]. The variation in the mitral regurgitation severity caused by the resynchronization therapy do not influence on predictive role of dP/dt . The limitation for using this parameter is the severity of the mitral regurgitation.

According to the literature in our study we showed significant correlation between basal and values of IVD and dP/dt with standard and optimal CRT conditions.

The treatment of significant dyssynchrony is a predictor of better hemodynamic recovery after CRT device implantation. Accordingly, there is significant reduction in end-diastolic diameter of the left ventricle after one year follow-up period with significant improvement in NYHA functional class and 6MWD.

In the majority of patients biventricular and left ventricle pacing with short or intermediate AV delay were the most optimal which is in accordance with previous studies [4, 14, 29]. In small number of patients left ventricular pacing was superior to the biventricular pacing modality. Left ventricular pacing alone may offer theoretical advantages over conventional biventricular pacing, requiring simpler systems that preserve intrinsic conduction via the right bundle branch, however as in previous studies we obtained the best results with biventricular pacing [30, 31]. In 8 (13%) patients optimal increased AV delay was 150 ms. The standard conditions were suitable in 25 (40,3%) patients. In all patients the standard CRT parameters lead to improvement, but with the optimization we achieved additional increase of dP/dt and decrease of IVD.

Mechanical asynchrony of the cardiac function has three determinants: atrioventricular (A-V) dyssynchrony, (V-V) interventricular dyssynchrony, and intraventricular dyssynchrony. Assessment of A-V dyssynchrony is currently used mainly in optimization procedures. However, there are studies demonstrating that each of those types of dyssynchrony may actually affect the outcome of resynchronization therapy. Interventricular dyssynchrony occurs when there is a significant delay between RV and LV activation, which can be crudely denoted by the presence of a wide QRS on the surface electrocardiogram.

Measurement of stroke volume derived from the left ventricular outflow tract velocity–time integral (VTI) of left ventricular outflow tract (LVOT VTI) has been proposed for optimizing both AV and VV delays [32]. On Figure 3 is echocardiographic presentation of AV optimization and on Figure 4 is shown echocardiographic presentation of VV optimization.

Conclusion

Echocardiography may play an important role in patient assessment before CRT and is currently one of the most commonly used non-invasive imaging modalities to provide information on its mechanical effects in heart failure patients. To make echocardiographic techniques a valuable addition also to the clinical field, further improvements in measurement feasibility and reliability, a better understanding of the effects of loading and wall stress, and multicenter validation are required.

The echocardiographic Doppler parameters, such as pre-ejection left/right ventricle interval, and their difference dP/dt are useful in selection of patients for the implantation of CRT and in process of setting the

optimal working conditions of this device. The variability in the echocardiographic Doppler parameters according to the conditions of the resynchronization pacemaker could be very useful in the assessment of the optimal treatment. Acute hemodynamic response assessed by echocardiography and expressed as dP/dt change improves the optimization process of this device. The individual

approach to optimization process leads to determination of the optimal conditions for each patient. Significant acute improvement could be achieved by optimization of the cardiac resynchronization. Echocardiographic assessment of the acute hemodynamic response to CRT in early post-implantation period could be useful predictor of long-term prognosis in patients with ischemic and non-ischemic cardiomyopathy.

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THE CLINICAL AND ECHOCARDIOGRAPHIC ANALYSIS OF NONCOMPACTION CARDIOMYOPATHY IN MISDIAGNOSIS AND MISSED DIAGNOSIS

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Aim. Echocardiography has become the main mean in detection of noncompaction cardiomyopathy (NCC). However, misdiagnosis and missed diagnosis were common. The aim of this paper was to analyze the misdiagnosis and missed diagnosis of NCC, improve the diagnostic accuracy of this disease.

Material and methods. We retrospectively analyzed the data of 56 subjects who had been clinically diagnosed with NCC in our institution, which included patients' total echocardiographic data since the disease onset. Echocardiographic data and cardiac magnetic resonance (CMR) data were compared with each other.

Results. 17 of the total subjects had been diagnosed with NCC after the first echocardiography at our institution. 39 subjects had not been diagnosed correctly until several times checking of echocardiography. 28 of them had been misdiagnosed as dilated cardiomyopathy (DCM) in local hospitals. All but 2 subjects were inconsistent between echocardiography measurement and CMR. The ratio of N/C was 2.63 ± 0.49 by CMR, and 2.55 ± 0.43 by echocardiography.

Conclusion. Echocardiography can be the first choice of NCC assessment for its advantages of being non-radiative, real-time, economic and characteristic. When the echocardiographic image is not typical in the early stage of NCC, a combination with CMR is necessary.

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Key words: noncompaction cardiomyopathy, echocardiography, cardiac magnetic resonance.

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КЛИНИЧЕСКИЙ И ЭХОКАРДИОГРАФИЧЕСКИЙ АНАЛИЗ СПОНГИОФОРМНОЙ КАРДИОМИОПАТИИ ПРИ ОШИБОЧНОМ ДИАГНОЗЕ И ПРИ ОТСУТСТВИИ ДИАГНОЗА

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Цель. Эхокардиография стала основным средством в обнаружении спонгиозной кардиомиопатии (NCC). Однако, ошибочный диагноз и отсутствие диагноза, были повсеместными. Целью данной работы является анализ случаев ошибочного диагноза и отсутствия диагноза NCC, чтобы улучшить точность диагностики этого заболевания.

Материал и методы. Мы ретроспективно проанализировали данные 56 пациентов, которые были клинически диагностированы с NCC в нашем учреждении, в исследование были включены полные данные эхокардиографические пациентов с момента начала заболевания. Эхокардиографические данные и данные сердечной магнитно-резонансной томографии (CMR) сравнивались друг с другом.

Результаты. 17-ти пациентам была диагностирована NCC после первого эхокардиографического исследования в нашем учреждении. 39 пациентов не были диагностированы правильно до тех пор, пока несколько раз не были проверены эхокардиографически. 28-ми из них была ошибочно диагностирована дилатационная кардиомиопатия (DCM) в местных больницах. Все данные, кроме 2-х пациентов, были совмещены между результатами эхокардио-

графии и CMR. Соотношение N/C 2.63 ± 0.49 было при CMR, и 2.55 ± 0.43 при эхокардиографии.

Заключение. Эхокардиография может быть первым выбором при NCC для оценки, вследствие следующих преимуществ: нерадиационный режим реального времени, экономические затраты и характеристика. Когда эхокардиографическое изображение не является типичным в ранней стадии NCC, то сочетание с CMR необходимо.

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Ключевые слова: спонгиозная кардиомиопатия, эхокардиография, сердечное магнитно-резонансное исследование.

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Introduction

Noncompaction cardiomyopathy (NCC) is a special and rare kind of inborn cardiomyopathy, which is also known as the spongy myocardium or myocardial sinusoidal persistent state [1–4]. It is characterized by excessive and prominent trabeculations associated with deep recesses that communicate with the ventricular cavity but not the coronary circulation [1–4]. The sponge-like meshwork of fibers and intertrabecular spaces used to be normal structures in the early embryonic development, and become compressed between the 5th and 8th weeks of fetal development [5]. NCC is thought to result from the arrest of myocardial compaction process during that period. It is also associated with other cardiac and systemic anomalies

[6]. Heart failure, thromboembolism and malignant ventricular arrhythmias are the most challenging clinical aspects of NCC [7–8], which contribute to the poor survival in these patients [9]. During the last decade, more attention had been paid to this condition, which resulted in an increased detection of NCC cases. However, studies in misdiagnosis and missed diagnosis about NCC were very limited. We retrospectively documented all clinical data and echocardiographic diagnosis of patients who were identified with NCC in our institution.

Material and methods

We retrospectively analyzed the subjects who had been clinically diagnosed with NCC from June 2010 to May

2013. 56 Han Chinese patients were referred to the Second Affiliated Hospital of Nanchang University, China. Informed consents were signed by each patient. We collected patients' total echocardiographic data in the hospital and the local hospitals since the disease onset. All patients were evaluated by medical history, physical examination, 12-lead electrocardiography (ECG), 2-D and doppler echocardiographic examination. Where clinically indicated, 24 h holter monitoring was performed, and all of the subjects accepted cardiac magnetic resonance (CMR) at the same time. Retrospective analysis of echocardiographic and CMR studies were performed by two fully blinded observers (Professor Yanna Liu with 35 years and associate professor Chunquan Zhang with 20 years of experience in imaging diagnosis). An analysis about the patient's total echocardiographic data in the hospital and local hospitals was performed. Echocardiographic data and CMR data were compared with each other. All volumetric measurements were individually performed twice by each observer.

Echocardiography

Comprehensive transthoracic echocardiography was performed by using a commercially available system (iU22, Philips Healthcare, Bothell, WA, USA) equipped with an S5-1 transducer (frequency transmitted 1.7 MHz, received 3.4 MHz), according to a standardized protocol. All images were analyzed offline using the Xcelera workstation (Philips Healthcare, KE, USA). Measurements relating to left heart size and function were performed in accordance with the American Society of Echocardiography (ASE) chamber quantification guidelines of 2006 [10]. Left ventricular (LV) long axis, short axis plane, apical 2-chamber plane and apical 4-chamber plane were used. The location of noncompaction was described by using a 16-segment model proposed by Manuel et al. [11] in Standardized Myocardial Segmentation and Nomenclature for Tomographic Imaging of the Heart. The apex was defined as caudal to the papillary muscles, while the base was defined as the area of the left ventricle cranial to the tips of the mitral valve, with the mid-segment being the area between these 2 segments. The apex was divided into 4 segments, while the base and mid-segment were divided into 6 segments each.

Diagnostic Criteria of LV Noncompaction

There are several definitions that attempt to describe the morphology of LV noncompaction. Although these definitions are available, the criteria proposed by Frischknecht et al. [12] and Stollberger et al. [13] are commonly used. It was reported that 68% of normal person could also have prominent trabeculations [14], however, more than 3 trabeculations were present in only 4% of individuals. Study showed that the combination of the two kinds of standard had a reasonable agreement with the features of NCC [15]. Therefore, in this study, we used

the two criteria together. Only when fulfilling them simultaneously, the diagnosis of NCC was confirmed.

- Segmental thickening of myocardial wall of left ventricle with two layers: a thin epicardial layer and a thick endocardial layer with prominent trabeculations and deep recesses. The ratio of noncompacted myocardium to compact myocardium at the end of systole is $> 2:1$ as shown in Figure 1.

- The trabeculations are usually located on the apical/lateral, middle/bottom walls of the left ventricle. Most noncompacted segments are hypokinetic. The flow between the intertrabecular recesses can be identified by using the color doppler method.

- Presence of more than three trabeculations in the LV wall, with the papillary muscles located at the apex, visible in one image plane.

Diagnostic Criteria of RV Noncompaction

The study of right ventricular (RV) noncompaction is still limited to isolated case reports until now [16, 17]. RV noncompaction was diagnosed in present study only in cases where a bilayered structure with flow within the trabeculae could be noted in the basal and middle wall of right ventricle, and the ratio of the bilayered structure must $> 2:1$.

CMR

All CMR exams were performed on a 3.0-T scanner (Signa EXCITE HDx, GE, WI, USA), using a dedicated 8-channel phased array surface cardiac coil. The scanning included black-blood sequences: double inversion recovery fast spin echo (DIRFSE), fat-suppression double inversion recovery fast spin echo (FSDIRFSE), white blood sequences (fast imaging employ steady state acquisition): echo time was 1,4 ms, repetition time 3,2 ms, field of view 35×28 cm, matrix 192×224 , flip angle 45° , slice thickness 6–8 mm, and bandwidth 125 kHz, perfusion CMR and late gadolinium enhancement (LGE) images. Scanning planes included LV short axis view, LV outflow tract view and long axis view, four-chamber view, two-chamber view, planned on short-axis pilots at 60° angles to each other to visualize all 16 segments according to the American Heart Association recommendation. LGE images in short-axis orientation were acquired for quantification of fibrosis 10 min after application of 0,2 mmol/kg/body weight gadopentetate dimeglumine using a three-dimensional T1-weighted inversion recovery turbo gradient echo sequence. Post-processing software Cardiac function parameters were analyzed offline, using MASS Analysis Plus V4.0.1 (Leiden University Medical Center and MEDIS medical imaging systems, Leiden, NL).

Here we used the ratio of $N/C > 2,3$ which was proposed by Petersen et al. [18] as diagnostic criterion. It produced a high sensitivity (86%) and specificity (99%) in the diagnosis of NCC: A the visual appearance of two distinct myocardial layers: a compacted epicardial layer

Table 1
Demographic and clinical characteristics of the study population

Characteristics	Number of the Patients
Male gender	39 (70%)
Age at diagnosis	49,2±13,4 years
Familial occurrence of sudden death	12
Facial dysmorphism	none
Smoking	8
Alcohol drinking	1
Diabetes	1
Shortness of breath	32 (57,1%)
Recurrent syncope	6 (10,7%)
Edema of the lower limbs	10 (17,9%)
No symptom	8 (14,3%)
Drug therapy	38 (67,9%)
Pacemaker/defibrillator	7 (12,5%)
Radiofrequency ablation	6 (10,7%)
Surgical repair of CHD	5 (8,9%)
NYHA I	10 (17,9%)
NYHA II	14 (25%)
NYHA III	27 (48,2%)
NYHA IV	5 (8,9%)

All values shown as number (%) or mean ± standard deviation.

Abbreviations: NYHA — New York Heart Association functional class, CHD — congenital heart disease.

and a non-compacted endocardial layer as shown in Figure 1; **B** the presence of marked trabeculation and deep intertrabecular recesses within the non-compacted layer; and **C** a non-compacted to compacted myocardial ratio of >2.3 as measured in end diastole in the long axis views.

Statistical Methods

Statistical analysis was performed by using SPSS software version 18.0 (SPSS Inc., Chicago, IL, USA). All continuous data were expressed as mean ± SD according to normal distribution of data in the Kolmogorov–Smirnov test. Categorical variables were expressed as frequencies and percentages. Continuous variables were compared by using the Student t-test. All statistical tests were two-sided. Only P-values < 0,05 were considered to be statistically significant.

Results

General Characteristics

A total of 56 Han Chinese patients were recruited. Their baseline characteristics are summarized in Table 1. Mean age of this cohort was 49,2 years, and 70% of them are male. 12 patients had family history of sudden death. 8 subjects had a history of smoking. Chest distress, shortness of breath, recurrent syncope, and edema of the lower limbs were the main symptoms of these patients. 8 patients had no obvious clinical manifestation. When the diagnosis was established, most patients were with standard anti-heart

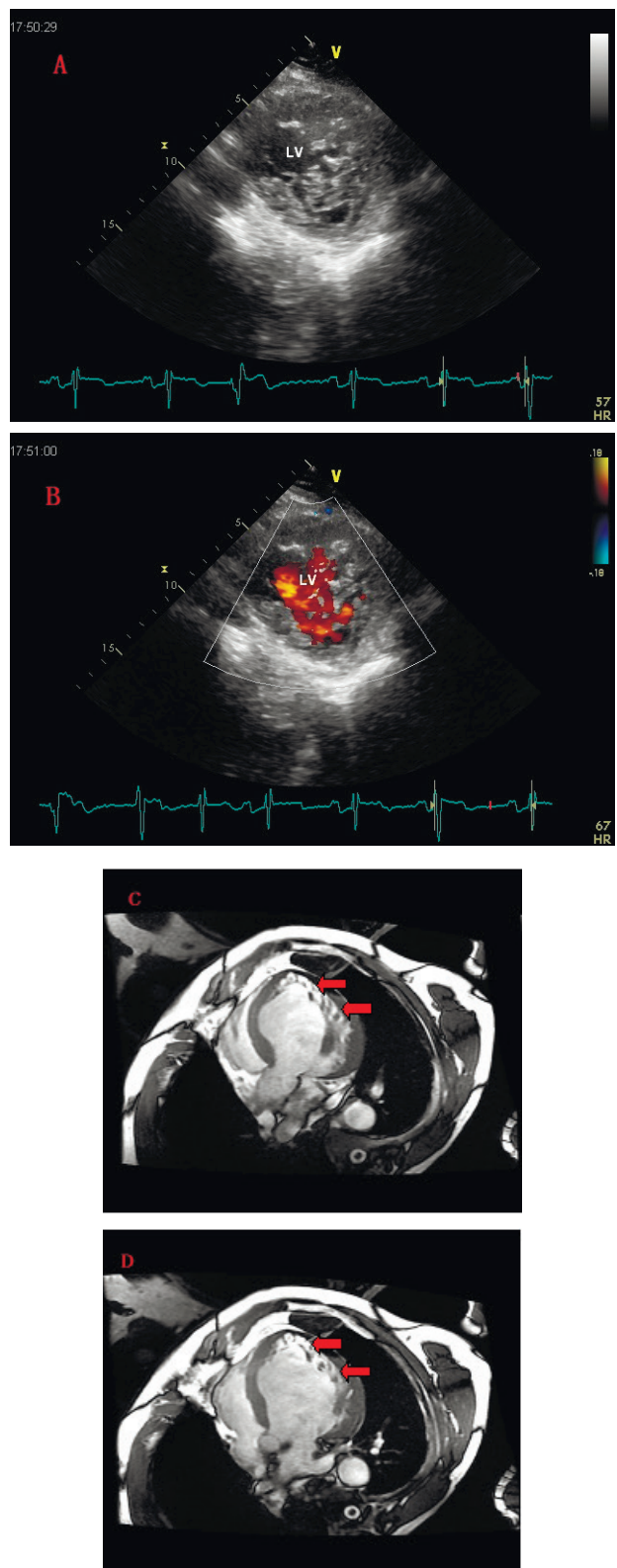


Figure 1. Left parasternal short-axis view at the level of left ventricular apex demonstrates extensive noncompaction (**A**). Short-axis view in which color doppler ultrasound is used to demonstrate flow within the trabeculae that originates from the ventricle cavity (**B**). White blood magnetic resonance images acquired in the LV outflow tract view (**C**) and the four chamber view (**D**). The LV apical, middle anterior and middle posterior trabeculation/non-compaction are clearly visualised (red arrowed).

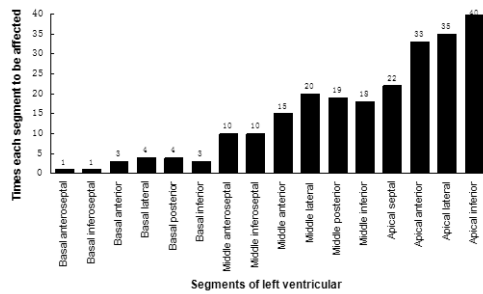


Figure 2. Distribution of left ventricular segments affected by noncompaction.

failure therapy (67,9%), and nearly half (48,2%) of the patients were New York Heart Association Class III at their first assessment. No patient had symptom or sign of facial dysmorphism. The average follow-up was 10 months and 1 case died of respiratory failure during this period.

Echocardiography

Referring to the total echocardiographic times the patients had received since the disease onset, we found that 17 of the 56 patients had been diagnosed with NCC after the first survey in our institution, accounting for 30% of the total subjects. The rest of 39 subjects hadn't been diagnosed correctly until they received several times checking of echocardiography, which were done mostly in local hospitals. Of the 39 subjects, 23 had received the examinations twice, 8 patients triple, 6 patients four times, 1 subject six times, and another one had underwent seven times before they had been finally diagnosed with NCC. The 39 subjects were treated with other diseases prior to our institution, where the diagnosis of NCC was made for the first time. 28 of the 39 subjects had been misdiagnosed as dilated cardiomyopathy (DCM) in the local hospitals, 3 subjects hypertensive heart disease, 2 subjects chronic myocardial infarction, 2 subjects sequela of myocarditis, 1 subject pulmonary heart disease, and 1 for hypertrophic cardiomyopathy. The rest of 2 patients with shortness of breath didn't found any obvious abnormality in the local hospitals.

54 of the total subjects were diagnosed with NCC by echocardiography at our institution, in which 50 subjects were LV noncompaction (LVNC), 3 subjects were RV noncompaction, and 1 was double ventricular noncompaction. The rest of 2 patients who had been diagnosed as DCM were finally proved to be NCC by CMR lately. Mean LV end-diastolic diameter of the cohort was 61,9 mm, and the mean LV ejection fraction was 41,1%, with severe global LV dysfunction (ejection fraction <30%) occurring in 9 patients. 10 patients had a normal ejection fraction. One complicated with left atrium thrombosis had been missed by two dimensional echocardiography checking, and finally was diagnosed by transesophageal echocardiography, as indicated in Table 2. 2 cases merged with atrial septal defect, 1 with atrial septal

Table 2

Left heart echocardiographic features of the studied population

Feature	Value
LVEDD, mm	61,9±13,1
LVSD, mm	49,7±13,9
IVSd, mm	9,2±1,8
LVPWd, mm	10±3,3
LVEF, %	41,1±15,0
LA volume, ml	39,7±8,8
LA thrombus, no	1
A-wave velocity (cm/s)	70,8±31,1
E-wave velocity (cm/s)	93,8±41,4
E/A ratio	1,6±0,9
N/C ratio	2,8±0,5

All values shown as number or mean ± standard deviation.

Abbreviations: LVEDD — LV end-diastolic diameter, LVESD — LV end-systolic diameter, IVSd — interventricular septal thickness at diastole, LVPWd — LV posterior wall thickness at diastole, LVEF — LV ejection fraction, LA — left atrium.

Table 3

The affected segmental comparison between echocardiography and CMR

Location of trabeculations	Echocardiography	CMR
Basal anteroseptal	2	0
Basal inferoseptal	2	2
Basal anterior	6	8
Basal lateral	4	6
Basal posterior	4	6
Basal inferior	6	6
Middle anteroseptal	10	6
Middle inferoseptal	10	4
Middle anterior	16	22
Middle lateral	20	24
Middle posterior	22	20
Middle inferior	18	20
Apical septal	20	20
Apical anterior	32	40
Apical lateral	24	30
Apical inferior	42	42

P = 0,80, there is no statistics significance in the affected segments between echocardiography and CMR.

defect and persistent left superior vena cava, 1 with ventricular septal defect and right coronary sinus tumor, and 1 with patent foramen ovale.

All 16 segments were evaluated successfully in all patients diagnosed with NCC. The most frequently involved segments were apical followed by the posterior, lateral and inferior mid-segments. The pathological myocardium in 16 regions was depicted in Figure 2. The base segment was very infrequently involved. All involved segments were equally hypokinetic compared with surrounding myocardium.

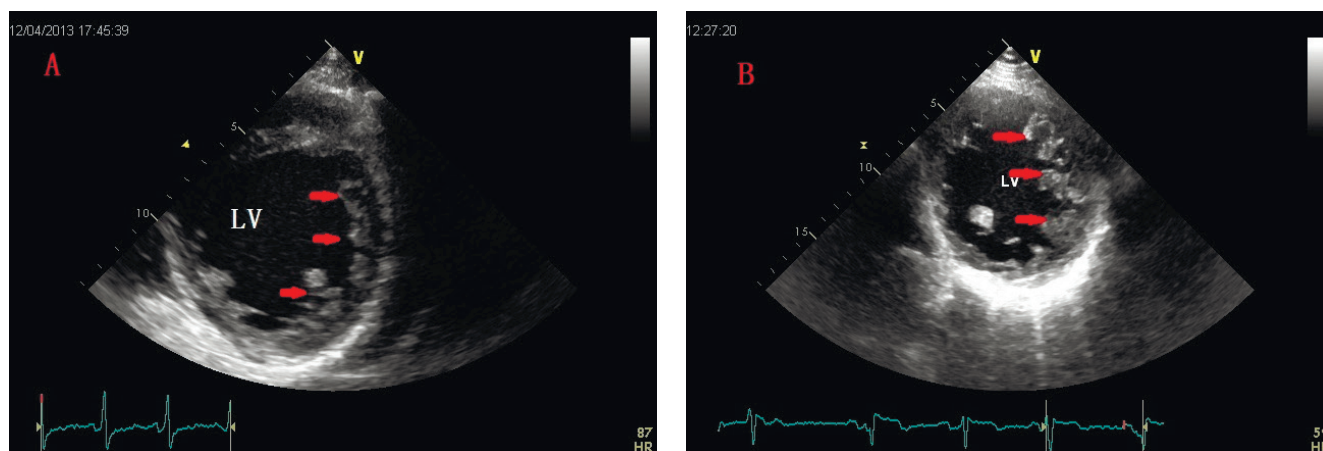


Figure 3. The pattern of inheritance in a family with pathological LV non-compaction. Systolic horizontal short-axis views of father (**B**) and son (**A**) show various degrees of non-compaction (red arrows). Ratio of N/C in **A** is 2.5, and 4.5 in **B**.

Comparison of Echocardiography with CMR in Imaging Data

All of the 56 subjects accepted echocardiography and CMR simultaneously. Of them, 2 patients had been diagnosed as DCM by echocardiography was proved to be NCC by CMR lately. Among the subjects who had consistent diagnosis, CMR showed 256 segments and echocardiography showed 238 segments which were affected by NCC, as indicated in Table 3. There was no significant difference between the capability of CMR and echocardiography to detect the segments which were affected by NCC ($P = 0,80$). The affected myocardium consisted of two layers: subendocardial noncompacted myocardium and epicardial compacted myocardium. The ratio measurement of N/C was $2,63 \pm 0,49$ by CMR, and $2,55 \pm 0,43$ by echocardiography.

Discussion

NCC is a rare disorder, which is considered to be an unclassified cardiomyopathy according to the World Health Organization [5, 19]. Most patients suffer a sudden death or underwent cardiac transplant within six years of diagnosis [5]. NCC is proved to be an autosomal dominant inherited cardiomyopathy [20]. It may be associated with G4.5 or ZASP1 mutation [21]. Mutations of the genes coding the epsilon 14–3–3 can also be the cause of embryogenesis myocardial compacted failure [22]. Endomyocardial biopsy examination is considered as the gold standard for the diagnosis of NCC [2, 5], whereas it is defective in its invasiveness, blindness and technical complexity in operation. Therefore, the diagnosis of NCC is usually made by using echocardiography, and increasingly MRI [1, 15]. This retrospective study in the Han Chinese patients firstly documented the specific misdiagnosis and missed diagnosis for NCC.

Due to it's mature technology, convenience, economy, and no radiation, echocardiography has been used as the main method to diagnose NCC [4, 5]. In this study, the

diagnostic rate of NCC was 96,4%, and the detection rate to other cardiac deformities is 100% by echocardiography. Numerous studies have confirmed that it can display the characteristic changes of NCC [1–5]. However, since the low incidence, and the diversity of clinical manifestations, most radiologists especially community doctors lack of a clear understanding to this disease, which leads the missed diagnosis and misdiagnosis rates of NCC to be very high. In present study, 70% of the patients had several times of echocardiography in local hospitals. Extension of the diagnostic period not only makes the treatment be delayed, also aggravates the economic burden of patients.

As NCC is a hereditary disease, the ultrasound doctors should ask in details about the patients' family or personal medical history before checking. Special emphasis must be placed on the patients who have a family history of NCC. An echocardiographic screening is required to their first-degree relatives when necessary. In present study, 12 patients had family history of sudden death, and 2 of them were parent-child relationship. Sudden cardiac death happened in 3 eldersisters of the father who was hospitalized because of chest tightness and shortness of breath for four years. When screening was carried out on the son who was clinically asymptomatic, we found that the LV myocardium in the apex was divided into two layers in which the ratio of N/C was 2.5 as indicated in Figure 3, and his heart function was normal. There is a general agreement that NCC can exist in isolation, but it may also coexist with other congenital heart [23] and neuromuscular [24] diseases. When NCC is found in a patient, we cannot satisfied with current diagnosis, and should scan carefully in multiple planes to exclude other malformations. 5 cases coexisted with other cardiac malformations in present study, and all of them were diagnosed by echocardiography. The blood flow between noncompacted myocardium is very slow and clogged, which allows mural thrombus to form. The lowest flow velocity between the noncompacted myocardium reached to 18 cm/s in present study. This

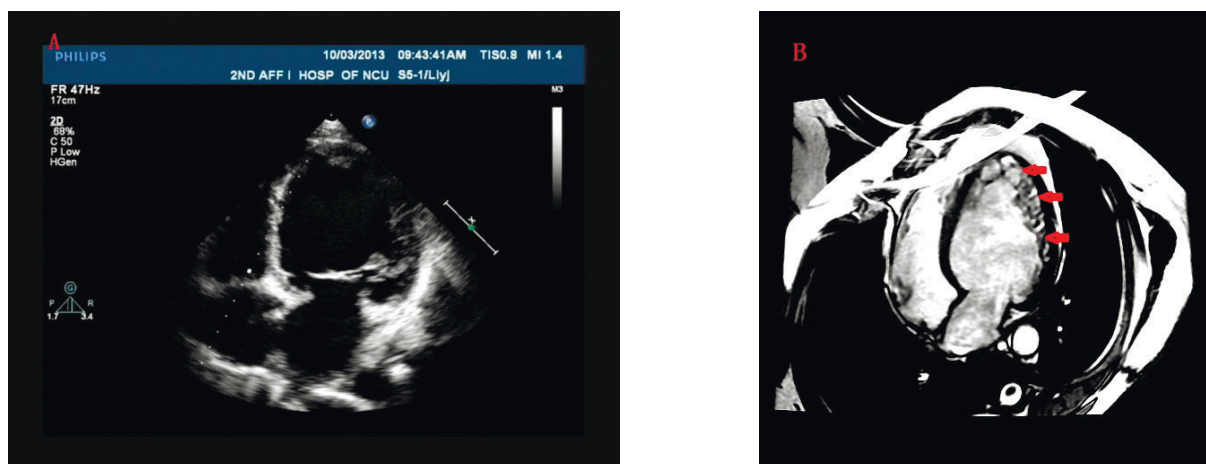


Figure 4. The apical 4-chamber plane, which was detected by echocardiography showed the enlargement of left ventricle, and the thickening of lateral wall was considered to be caused by DCM (A). But CMR showed trabeculation and deep intertrabecular recesses (B), LGE didn't find any abnormal enhancement within the myocardium, and made the diagnosis of NCC.

kind of thrombus adds a wall falls off easily form embolus, produces viscera embolism with dangerous. In present study, 1 case coexisted with left atrial thrombus. We did not find it in conventional echocardiography, and it was finally diagnosed by transesophageal echocardiography.

Studies indicated that hypertrophic trabecular could also be found in the heart of normal people [14], but the ratio of N/C was <2 . Therefore, the diagnosis of NCC should be cautious. We must rule out other congenital or acquired heart diseases such as DCM before the diagnosis was set up. Measurements and ratios must be integrated with clinical, pathophysiologic and evolving genetic variables to make an accurate diagnosis, and avoid overdiagnosis. A pathoanatomic study also found more than 3 trabeculations were present in only 4% of individuals [1]. Thus in present study, we used two echocardiographic definitions to identify NCC, which assessed the number and size of trabeculations, as well as the relative thickness of the non-compacted layer. Thus, we believe that we have avoided overdiagnosis to the most extent. Cardiac enlargement and cardiac function decline are the common performance in NCC and many other kinds of heart diseases. The key to differentiate them is to follow the diagnostic criteria of NCC strictly, that is particularly important as the morphologic appearance of increased trabeculations may be produced if oblique views of the ventricle are used for detecting [15]. Present study found that NCC was most probable to be misdiagnosed as DCM, accounting for 50% of the total cases. Essentially there are several important differences among them. DCM is mainly characterized by ventricular chamber enlargement, ventricular wall becomes thin evenly, and endocardium is smooth [25]. It was reported that the expansion tended to be more spherical, and the hypertrophic trabecular located in the lateral wall of LV more often in DCM [26]. However, NCC usually have several segments that are noncompacted, apex is the segment which is the most easy to be affected.

[1] The pathological change of NCC is endomyocardial fibrosis [5], while the typical myocardial fibrosis in DCM mostly happen in the mid-myocardium of the basal septum [27]. NCC must also be differentiated from diseases that may lead to obstruction of the outflow of the left ventricle, such as hypertensive heart disease, aortic valve lesion etc. All NCC imitators should be considered when making a diagnosis.

NCC is predominantly a genetic cardiomyopathy with variable clinical presentations ranging from asymptomatic to severe [28]. Parts of the patients are asymptomatic or only have mild symptoms for many years. Heart function can also be within normal range, and clinical diagnosis is therefore difficult. More attention should be paid to this situation when checking, observing myocardial situation from the bottom to the apex of the heart carefully, zooming in the suspicious segment partially.

RV noncompaction is especially rare [15]. In this study we reported 3 cases of RV noncompaction and a biventricular noncompaction. As trabeculation is the normal anatomic structure of RV apex, which runs from the septum to the apex, it is difficult to define RV noncompaction. Thus, we used a bilayered myocardial segment in the basal and middle wall, whose ratio must be $>2:1$ as standards defined.

Due to the multiple positions and sequences, high soft-tissue resolution and spatial resolution, CMR is being used in diagnosis of NCC gradually [29, 30]. Studies show that CMR can display the pathological cardiac muscle more clearly, and is easier to detect the apex and lateral wall of left ventricle [29–31]. Because of highly variable LV trabeculation, qualitative or even semi-quantitative parameters to differentiate normal compaction of the myocardium in healthy subjects from NCC or from other cardiomyopathies like DCM or hypertrophic cardiomyopathy (HCM) might be difficult by using echocardiography. AS LGE affords high quality myocardial

definition. It has been used as a gold-standard in the identification and characterization of cardiac masses and cardiomyopathies. It can also identify the internal structure of myocardium, distinguish fibrotic myocardium from the normal one [31–32].

Grothoff et al. [20] found that none of the NCC patients demonstrated intramyocardial LGE, however, LGE was found in all DCM and HCM patients. The findings were same as other studies that also stated a lack of LGE in NCC [33, 34].

What's more, the phase-sensitive inversion recovery sequence has shown advantages in visualization of fibrosis in regard to image quality and reproducibility compared with standard magnitude detection [35]. It can clearly show the location and scope of myocardial fibrosis and may have prognostic implications [2]. In present study, all subjects were found fibrosis, which located under the endocardium. 2 of them were diagnosed as DCM by echocardiography firstly, but CMR showed that the myocardial fibrosis located under the endocardium, and proved that they were not DCM but NCC, as displayed in Figure 4. However, CMR is expensive, and has many contraindications. The patients who have cardiac

pacemaker, metal dentures or those who suffer from claustrophobia and cardiac surgery can't accept CMR examination [36]. What's more, most of the NCC patients have cardiac insufficiency. The patients cannot lay down and control their breath for a long time, which will make the quality of CMR image very poor. Therefore, the application of CMR is limited.

There are some limitations in this study. Firstly, larger samples are necessary to evaluate trabecular patterns and further refine the ability to diagnose NCC. Secondly, as the main clinical manifestation of these patients is heart failure, a long-term follow-up to them is needed to assess the patient's prognosis. Finally, we have not addressed the issue of myocardial biopsy and genetic testing, which is an important future research and highly relevant clinical consideration.

Conclusion

Echocardiography can be the first choice of NCC assessment for its advantages of being non-radiative, real-time, economic and characteristic. When the echocardiographic image is not typical in the early stage of NCC, a combination with CMR is necessary.

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RELATIONSHIP OF TNF- α -308, IL-10-1082 GENE POLYMORPHISMS WITH THE SEVERITY AND SUSCEPTIBILITY OF RHEUMATIC HEART DISEASE IN TURKISH CHILDREN

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Aim. Acute rheumatic fever is an inflammatory disease developing after upper respiratory tract infection with group A streptococci and its most important complication is rheumatic heart disease (RHD). Tumor necrosis factor (TNF)- α and interleukin (IL) -1-1082 gene polymorphisms were associated with susceptibility to develop rheumatic heart disease. The aim of our study is to determine the frequency of IL-10-1082 A/G and TNF- α -308 G/A gene polymorphism in Turkish population and to investigate the relationship between these polymorphisms and rheumatic heart disease.

Material and Methods. Genotypes of 57 unrelated children with rheumatic heart disease and 99 controls were determined by use of PCR-RFLP.

Results. No significant differences were found in genotypes or allele frequencies of TNF- α -308 and IL-10-1082 genes between RHD and control group. There was no relation between TNF- α -308 genotype and allele distribution with valvular involvement ($p>0.05$). IL-10-1082 GG and AG genotypes were seen more frequent in patients with multiple valvular disease but there was no statistical significance ($p>0.05$).

Conclusion. As a result, there was no relationship between TNF- α -308, IL-10-1082 gene polymorphisms and rheumatic heart disease or valvular involvement in the study population ($p>0.05$). Our results are thought that TNF- α -308 polymorphisms are silent and may become important only with some certain HLA alleles. Further studies checking both cytokine polymorphism and HLA alleles are needed.

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Key words: polymorphism, rheumatic heart disease, IL-10-1082, TNF- α -308.

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IL — interleukin, RF — rheumatic fever, RHD — rheumatic heart disease, SNP — single nucleotide polymorphisms, TNF — tumor necrosis factor.

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ОТНОШЕНИЯ ПОЛИМОРФИЗМОВ ГЕНОВ TNF- α -308 И ИЛ-10-1082 С ТЯЖЕСТЬЮ И ВОСПРИИМЧИВОСТЬЮ К РЕВМАТИЧЕСКОЙ БОЛЕЗНИ СЕРДЦА У ТУРЕЦКИХ ДЕТЕЙ

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Цель. Острая ревматическая лихорадка — это воспалительное заболевание, которое развивается после инфицирования верхних дыхательных путей группой стрептококка А и его важнейшими осложнениями являются ревматические пороки сердца (РПС). Фактор некроза опухоли (TNF) - α и интерлейкин (IL) -1-1082 полиморфизмы генов были связаны со склонностью к развитию ревматической болезни сердца. Целью нашего исследования является определение частоты генного полиморфизма IL-10-1082 A/G и TNF- α -308 G/A у турецкого населения, и исследование отношений между этими полиморфизмами и ревматической болезнью сердца.

Материал и методы. Генотипы 57 неродственных детей с ревматическими пороками сердца и 99 детей (группа контроля) были определены с использованием ПЦР-ПДРФ.

Результаты. Не обнаружено значимых различий в генотипах или частоте аллеля TNF- α -308 и IL-10-1082 генов между РПС и контрольной группой. Не было никакой связи между генотипом TNF- α -308 и аллелью распределение с вовлечением клапанов ($p>0.05$). Генотипы IL-10-1082 GG и AG наблюдались

чаще у больных с множественными клапанными пороками, но не было никакой статистической значимости ($p>0.05$).

Заключение. Как следствие, не существует никакой связи между полиморфизмами генов TNF- α -308, IL-10-1082 и ревматической болезнью сердца или вовлечения клапанов в исследуемой популяции ($p>0.05$). Наши результаты предполагают, что полиморфизмы TNF- α -308 неактивны и могут стать актуальными только при некоторых определенных аллелях HLA. В дальнейших исследованиях необходима проверка обоих цитокинов и полиморфизма аллелей HLA.

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Ключевые слова: полиморфизм, ревмокардит, IL-10-1082, TNF- α -308.

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Introduction

Rheumatic heart disease (RHD) is an inflammatory disorder and autoimmune sequel of group A streptococcal infection complicated by rheumatic fever (RF). Autoimmunity induced by antigenic mimicry between the streptococcal glycoprotein and human cardiac myosin may be responsible for the pathogenesis of RHD [1]. High familial incidence of RF suggests that genetic factors play a role in susceptibility to RF and RHD. RF is still public health burden in Turkey as in developing countries [2].

Cytokines appear to play a critical role in triggering inflammatory and immunologic reactions in RF. Increase

in tumor necrosis factor (TNF) - α and interleukin (IL) -1 levels in patients with RF and RHD have been known for a long time [3]. Even, that IL-1 α in carditis and IL-6 in arthritis may be helpful as minor criteria for diagnosis of RF has been considered [4]. IL-10 is another important immunoregulatory cytokine. The biological actions are mainly inhibitory including inhibition of pro-inflammatory cytokines [5].

Single nucleotide polymorphisms (SNPs) in regulatory regions of cytokine genes can lead to the susceptibility and onset of diseases. The human TNF- α gene is located in the HLA region of human chromosome 6 and contains several

polymorphic sites. TNF- α biallelic SNPs at position -238, -308, and -376 with respect to the TNF transcriptional start site are all substitutions of adenine (A) for guanine (G) [6]. Several SNPs in the promoter region of IL-10 have been described but one of the the most investigated are located at positions -1082 of the transcriptional start site [5]. In RHD, a relationship between TNF- α -308, and IL-10-1082 polymorphisms and multivalvar involvement has been determined [4]. Since cytokine gene polymorphisms are specific on the basis of population, there are very few studies about TNF- α -308 and IL-10-1082 gene polymorphism in Turkish children with RF of which results have also been conflicting. The aim of our study is to find out the possible influences of IL-10-1082 A/G and TNF- α -308 G/A gene polymorphisms on RHD development. Besides; on the basis of our sample, to determine the allele and genotype frequencies of IL-10-1082 A/G and TNF- α -308 G/A polymorphisms in Turkish population are also aimed.

Material and Methods

Patients

This study included 57 unrelated children with RHD recruited from the pediatric cardiology department at the Mersin University Medical Faculty. Patients were diagnosed according to Jones' modified criteria and the lesions of RHD were confirmed by echocardiography. The control group consisted of 99 healthy unrelated children diagnosed with innocent murmur who had normal echocardiography. The genotyping success rate was 97.8% for the TNF- α -308 polymorphism and 88.0% for the IL-10-1082 polymorphism. Demographic characteristics, personal or family history of rheumatic fever, and echocardiographic results were obtained from the groups. The exclusion criteria for control group consisted of subjects who have history of rheumatic fever or related persons. Besides, the subjects with the history of other autoimmune associated diseases were excluded. This study had received Ethical Approval from the Mersin University Medical Faculty Ethics Committee and inform consents were given.

Genotype Analyses

Genomic DNA was extracted by the standard phenol-chloroform methods from peripheral blood leukocytes. The polymorphisms were analyzed by using of PCR/RFLP. The primary sequences for the TNF- α -308 forward and reverse primaries were (5'-AGGCAATAGGTTTTGAGGGCCAT-3') and (5'-TCCTCCCTGCTCCGATTCCG-3'), respectively. In order to characterize the IL-10-1082 polymorphism, forward (5'-CTCGCTGCAACCCAACTGGC-3') and reverse (5'-TCTTACGCAACCCAACTGGC-3') primaries were used. PCR amplification was performed in a final volume of 23 μ l containing 30 ng genomic DNA, 50 pmol of each TNF- α -308 and IL-10-1082 primaries, 0.2

mM dNTPs, 1XPCR buffer with (NH₄)₂SO₄, 2.5 mM MgCl₂, 10% DMSO, and 2.0 U of Taq DNA polymerase (Sigma-D4545).

The PCR conditions for the TNF- α -308 gene were initial denaturation at 96 °C for 2 min, 35 cycles of denaturation for 45 s at 96 °C, annealing for 1 min at 60 °C, and extension for 90 s at 72 °C, terminated by a 7 min elongation at 72 °C. The 107 bp PCR product was digested with *Nco*I restriction endonuclease (MBI, Fermentas, Vilnius, Lithuania) for overnight at 37 °C. The PCR conditions for the IL-10-1082 gene were initial denaturation at 95 °C for 5 min, 35 cycles of denaturation for 30 s at 95 °C, annealing for 45 s at 60 °C, and extension for 30 s at 72 °C, terminated by a 7 min elongation at 72 °C. The 139 bp PCR product was digested with *Mn*II restriction endonuclease (MBI, Fermentas, Vilnius, Lithuania) for overnight at 37 °C. The digestion products were electrophoretically separated on a 3% agarose gel and visualized using ethidium bromide staining.

Statistical analysis

Continuous variables were presented as mean $\pm$ standard deviation and categorical variables as numbers and percentages. The "independent sample t-test" was used for comparison of continuous variables between case group and control group. The distribution of genotype and allele frequencies between cases and controls was compared using the "chi-square test".

We calculated odds ratios and 95% confidence intervals using logistic regression. The allele and genotype frequencies are in "Hardy-Weinberg equilibrium". Statistical analyses were performed by use of the computer software SPSS for Windows, version 11.5 and the value of $p < 0.05$ was considered statistically significant.

Results

Clinical characteristics

Our study population consisted of 57 RHD patients (27 female, 30 male) and 99 age-matched healthy control subjects (43 female, 56 male) without a history of heart failure. The mean age of the patients was 12,2 $\pm$ 2,5 years (range, 7-18 years) and the mean age of the control group was 12,0 $\pm$ 2,7 years (range, 7-17 years).

Demographical characteristics of the patients and controls are shown in Table 1. There were no significant differences in age, gender and socio-economic status, between the patients and controls. It is remarkable that positive family history of RHD was present in 19% of cases. Depending on the exclusion criteria, no family history has been reported in the control group. Carditis were only major manifestation of the disease in most of the patients. While 21 patients had arthritis and 3 patients had Sydenham's chorea as well as carditis. On the basis of valvular involvement, 16 (28,1%) patients had mitral regurgitation, 10 (17,5%) had aortic

Table 1

Demographical characteristics of patients and controls

	Patients (n=57)	Controls (n=99)	p
Age (year)	12,19±2,51	12,01±2,66	0,625
Gender (F/M) (%)	27 (47,4) / 30 (52,6)	43 (43,4) / 56 (56,6)	0,738
Parental consanguinity (%)	15 (26,3)	30 (30,3)	0,714
Family history of RF	19 (33,3)	-	-
Low socioeconomic status	28 (49,1)	40 (40,4)	0,318

Abbreviations: F — female, M — male, RF — rheumatic fever.

Table 2

Allele and genotype frequencies of TNF- α -308 and IL-10-1082 in patients and controls

	Patients (n=57)	Controls (n=97)	P	OR	95% CI
TNF-α-308					
Genotypes					
GG (%)	45 (78,9)	64 (66)		1,0 (ref)	
AG (%)	12 (21,1)	30 (30,9)	NS	0,569	0,263–1,230
AA (%)	0	3 (3,1)	NS	0,202	0,010–4,017
Alleles					
G (%)	102 (89,5)	158 (81,4)	NS	1,937	0,963–3,897
A (%)	12 (10,5)	36 (18,6)	NS	0,516	0,257–1,039
IL-10-1082					
Genotypes					
AA (%)	28 (51,9)	33 (40,2)		1,0 (ref)	
AG (%)	21 (38,9)	40 (48,8)	NS	0,618	0,298–1,283
GG (%)	5 (9,3)	9 (11)	NS	0,654	0,196–2,180
Alleles					
A (%)	77 (71,3)	106 (64,6)	NS	1,359	0,803–2,299
G (%)	31 (28,7)	58 (35,4)	NS	0,736	0,435–1,245

Abbreviations: OR — odds ratio, 95% CI — 95% confidence intervals, NS — not significant.

regurgitation and 31 (54,4%) had both aortic and mitral regurgitation.

TNF- α polymorphism analysis

The genotypic and allelic distributions of TNF- α -308 and IL-10-1082 polymorphisms for cases and controls are shown in Table 2. The frequencies of G and A alleles for the TNF- α -308 gene were 89,5% and 10,5% in the cases and 81,4% and 18,6% in the controls, respectively. These differences were not significant. Among the cases, the prevalence of the GG, AG and AA genotypes were 78,9%, 21,1% and 0%, while it was 66%, 30,9% and 3,1% among the controls, respectively. The homozygous AA genotype was not observed in cases our study. Significance of the deviation of observed genotype frequencies from those predicted by the Hardy-Weinberg law was determined using χ^2 analysis in both groups ($p=0,001$). No considerable differences were observed in allele or genotype frequencies for the IL-10-1082 gene between RHD and controls. The frequencies of A and G alleles for the IL-10-1082 gene were 71,3% and 28,7% in the cases whereas 64,6% and 35,4% in the controls, respectively.

The frequencies of the AA, AG, and GG genotypes in the control and case groups were 51,9%, 38,9%, and 9,3%, and 40,2%, 48,8%, and 11%, respectively. The genotype distributions were in accordance with the Hardy-Weinberg equilibrium among patient group and control group ($p=3,15$ and $p=0,58$, respectively).

We also analyzed relation between genotype and allele distribution of TNF- α -308 and IL-10-1082 gene polymorphism with valvular involvement (Table 3). However, there was no relation between TNF- α -308 genotype and allele distribution with valvular involvement ($p>0,05$). IL-10-1082 GG and AG genotypes were observed more frequently in patients with multiple valvular disease but there was no statistical significance ($p>0,05$).

Discussion

In many autoimmune diseases, the role of TNF- α and IL-10 was investigated [7, 8]. In general, the effect of TNF- α is pro-inflammatory, IL-10 is immunosuppressive and anti-inflammatory. Especially, TNF- α has an active role in the pathogenesis of rheumatic diseases. Besides, in

Table 3

Allele and genotype frequencies of TNF- α -308 and IL-10-1082 in patients with different valve damage

	SVL	MVL	P	OR	95% CI
TNF-α-308	(n=26)	(n=31)			
Genotypes					
GG (%)	21 (80,8)	24 (77,4)	NS	0,816	0,225 $\pm$ 2,961
AG (%)	5 (19,2)	7 (22,6)	NS	1,225	0,338 $\pm$ 4,443
AA (%)	0	0			
Alleles					
A (%)	5 (9,6)	7 (11,3)		1,196	0,356 $\pm$ 4,019
G (%)	47 (90,4)	55 (88,7)		0,836	0,249 $\pm$ 2,808
IL-10-1082	(n=25)	(n=29)			
Genotypes					
AA (%)	15 (60)	13 (44,8)		1,0 (ref)	
AG (%)	9 (36)	12 (41,4)	NS	1,538	0,492 $\pm$ 4,808
GG (%)	1 (4)	4 (13,8)	NS	4,610	0,456 $\pm$ 46,673
Alleles					
A (%)	39 (78)	38 (65,5)	NS	0,536	0,227 $\pm$ 1,267
G (%)	11 (22)	20 (34,5)	NS	1,866	0,789 $\pm$ 4,413

Abbreviations: OR — odds ratio, 95% CI — 95% confidence intervals, SVL — single valvular lesions (mitral or aortic), MVL — multivalvular lesions, NS — not significant.

the cases of inflammatory involvements of the heart, the level of TNF- α has been increased [3]. It has also been demonstrated that TNF- α -308 polymorphism is associated with high TNF- α production [9]. Due to the fact that, several studies have been conducted to evaluate the association of the TNF- α -308 gene polymorphism and RHD. The results, however, are conflicting. One study has showed that A allele (OR=10,8) and AG genotype (OR=9,85) have been associated with RHD [10]; on the other hand, borderline association between RHD and TNF- α -308 gene polymorphism (OR=1,4) has been reported [11]. In addition, this study showed that TNF- α -308 polymorphism was related to the development of mitral valve lesions in a cohort of Brazilian RHD patients (OR=1,9) [11]. Furthermore, Settin et al. [4] demonstrated that all RHD cases had a significantly higher frequency of AA genotype of TNF- α -308 gene polymorphism (OR=5,7). Recently, Rehman et al. [12] observed that the TNF- α -308 AA and GA genotypes were associated with susceptibility to RHD (OR=9,94 and OR=1,97, respectively). There is only one study in the Turkish population where an association of TNF- α -308 A allele with RHD has been observed (OR=3,3) [13]. On the other hand, in two studies from Turkey no differences in the distribution of genotypes between cases and controls were observed [14, 15], and these results were similar to those of our study.

In the literature, there are only three studies on the association of IL-10-1082 gene polymorphism with RHD of which results were controversial. Settin et al. [4] found that the frequency of AA and GG genotypes was higher in RHD than controls, which supported a role for the IL-10-1082 polymorphism in determining the risk of

RHD. Rehman et al. [12] reported that no association was found between IL-10-1082 polymorphism and susceptibility to RHD. Another study from Turkey reported no association between IL-10-1082 genotype and RHD, which are similar to our results [15].

Previous studies examined associations between TNF- α -308 and IL-10-1082 polymorphisms with valvular involvement. We did not find an association between the TNF- α -308 and IL-10-1082 polymorphisms and valvular involvement in the Turkish population. An association between TNF- α -308 polymorphism and patients with multivalvular disease in a Mexican population has been reported. The TNF- α -308 AG genotype and A allele frequencies were increased in patients with multivalvular disease when compared controls (OR=14 and OR=11,7, respectively). There was also increased frequency of TNF- α -308 A allele in patients with multivalvular lesion (OR=8.65) [10]. Settin et al. [4], reported that valvular involvement is associated with TNF- α -308 and IL-10-1082 polymorphisms in the Egypt population. They found that increased frequencies of genotypes TNF- α -308 AA, GG with IL-10-1082 GG in cases with multivalvular disease. Also genotypes AA of both TNF- α -308 and IL-10-1082 were increased in patients with multivalvular lesions.

Conclusion

In this study, which was conducted in a Mersin sample, the results have demonstrated that IL-10-1082 A/G and TNF- α -308 G/A gene polymorphisms had no influence on the risk of RHD development. Besides, no relationship between TNF- α -308 and IL-10-1082 gene polymorphisms

with RHD and valvular involvement was detected. The rates of allele and genotypes of control group contribute to determine the frequencies of these polymorphisms in Turkish population.

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THE PREVALENCE OF CONGENITAL HEART DISEASES AMONG ROMANIAN CHILDREN — EXPERIENCE OF A SINGLE CENTER

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Aim. Congenital heart defects (CHD) are the leading cause of infant mortality becoming an important public health problem. Time trends in CHD by specific phenotype and with long follow-up time are rarely available for a large pediatric population.

Material and methods. We present the prevalence of CHD over the past 5 years among Romanian children. Individuals with CHDs were classified by several criteria including type of pathology, association of the pathology with various syndromes and abnormalities, postnatal complications or treatment.

Results. The overall CHD birth prevalence increased. Generally, prevalence increased for defects diagnosed in infancy and preschoolers patients. Isolated septal defects such as atrial septal defect (ASD) was present in 29,69% of patients while transposition of the great vessels was present in 1,87% of children, respectively. Among the severe defects, tetralogy of Fallot — atresia/hypoplasia of the pulmonary artery association showed the largest prevalence. Considering the syndromic CHD, the highest incidence (78,78%) was recorded for Down syndrome, followed by Turner syndrome. The most frequent postnatal complication in CHD patients was cardiomegaly, followed by pulmonary hypertension. Only 29,94% of the patients underwent corrective surgery, the rest remained on medication. The highest incidence rate was recorded for tetralogy of Fallot (42,85%), followed by isolated septal defects. On average, tetralogy of Fallot cases were operated on 16,6 months after diagnosis while transposition of the great vessels after 2,5 months.

Conclusion. The increasing prevalence of CHDs reported was confirmed in the present study. This is mostly due to an increasing number of isolated septal defects diagnosed in infancy. In the future, the etiology of CHD needs to be further clarified

and prospective birth defect registries covering the a large population are needed to determine the exact birth prevalence of CHD.

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Key words: congenital heart disease, prevalence, children, syndrome, pregnancy.

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ASD — atrial septum defect, CHD — congenital heart diseases, VSD — ventricular septum defect, GUCH — grown-up congenital heart disease.

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РАСПРОСТРАНЕННОСТЬ ВРОЖДЕННЫХ ПОРОКОВ СЕРДЦА СРЕДИ РУМЫНСКИХ ДЕТЕЙ — ОПЫТ ОДНОГО ЦЕНТРА

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Цель. Врожденные пороки сердца (CHD), являющиеся ведущей причиной младенческой смертности, становятся важной проблемой общественного здравоохранения. Тенденцией последнего времени в области диагностики CHD направлены на конкретный фенотип и по причине длительного времени наблюдения редко бывают доступны для большей части детского населения.

Материал и методы. Мы представляем распространенность CHD за последние 5 лет среди румынских детей. Лица с CHD были классифицированы по нескольким критериям, в том числе вида патологии, ассоциации патологии с различными синдромами и аномалиями, послеродовыми осложнениями или лечением.

Результаты. Общее количество CHD при рождении увеличилось. В целом, увеличилась распространенность диагностирование пороков у младенцев и дошкольников. Изолированные септальные пороки, такие как дефект межпредсердной перегородки (ASD) присутствовали у 29,69% пациентов, тогда как транспозиция магистральных сосудов присутствовала у 1,87% детей, соответственно. Среди серьезных дефектов, тетрада Фалло — ассоциация атрезия/гипоплазия легочной артерии проявила наибольшую распространенность. Учитывая симптоматические CHD, наиболее высокий уровень заболеваемости (78,78%) был отмечен для синдрома Дауна, сопровождаемого синдромом Тернера. Из наиболее частых послеродовых осложнений у больных CHD наблюдалась кардиомегалия, затем легочная гипертензия. Только 29,94%

пациентов, были подвергнуты хирургическим операциям, остальные оставались на лекарственной терапии. Наивысший уровень заболеваемости был отмечен при тетраде Фалло (42,85%), а также изолированных септальных пороках. В среднем, больные с тетрадой Фалло были прооперированы через 16,6 месяцев после установления диагноза, в то время как с транспозицией магистральных сосудов через 2,5 месяцев.

Заключение. Сообщение о растущем преобладании CHD было подтверждено в настоящем исследовании. Это произошло, в основном, за счет увеличения количества изолированных септальных дефектов, диагностируемых в младенчестве. В будущем, этиология CHD нуждается в дальнейшем уточнении и создание перспективных реестров дефектов при рождении, охватывающих большие группы населения, необходимо для определения точной распространенности CHD.

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Ключевые слова: врожденный порок сердца, распространенность, дети, синдром, беременность.

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Introduction

Congenital heart diseases (CHD) are the most common cause of congenital anomalies being an increasing health problem. Twenty-eight percent of all major congenital anomalies consist of heart defects [1]. CHD comprises a wide range of cardiovascular malformations from critical forms presenting in the immediate newborn period to mild defects which may not be detected until adulthood [2]. The birth prevalence of CHD is estimated to 8 per 1,000 live births [3]. Nowadays, the cardiovascular diagnostics and cardiothoracic surgery have improved, leading to an increased survival of newborns with CHD. Thus, a lot of patients with CHD reach adulthood. The prevalence of CHD is estimated to be 4 per 1,000 adults [4], the number of adults with CHD exceeding the number of affected children [5]. Despite remarkable progress in the clinical care there are major challenges regarding the management of CHD, which remains the leading cause of infant mortality among birth defects [6]. In our study, we aimed to evaluate the prevalence of CHD in Romanian children admitted in our hospital.

Material and methods

We carried out a descriptive study over a period of five years (2007–2012) on patients admitted in the Department of Pediatrics II Cluj-Napoca, Romania. We enrolled 266 children diagnosed with congenital heart defects based on their echocardiographic examination. The inclusion criteria were the maximum age of 18 years at the diagnostic and the need for corrective surgery.

The following data was taken into account: type of pathology, association of the pathology with various syndromes and abnormalities, postnatal complications or treatment.

The study was approved by the local Committee of Ethics of the University of Medicine and Pharmacy of Cluj-Napoca. Informed consent was obtained from parents or legal tutors at the moment of admission to hospital in compliance with the principles of the Helsinki Declaration.

Statistical analysis was performed using Statistical Package for Social Sciences (SPSS) 21.0 for Windows for a descriptive analysis of the population. Results were expressed as means $\pm$ standard deviations.

Results

Mean patients age was $3,66 \pm 4,60$ years (male: female = 151:115). The following age groups are taken into account:

- 0–1 month: newborn (27 patients)
- 1–12 months: infant (92 patients)
- 12 months — 36 months: toddler (37 patients)
- 36 months — 72 months: preschooler (45 patients)
- 72 months — 120 months: older child (39 patients)
- 120 months — 168 months: puberty (13 patients)
- >168 months: adolescence (13 patients).

Table 1

Types of congenital heart defects

Type of defect	Number
Atrial septum defect	79
Ventricular septum defect	40
Tetralogy of Fallot	30
Patent ductus arteriosus	27
Valvular defects	40
Common atrioventricular canal	14
Coarctation of the aorta	10
Transposition of the great vessels	5
Others	21

78,19% (208) mothers had a normal evolution of the pregnancy, whereas 21,80% (58) had coexisting conditions or abnormalities. The main events that caused the abnormal progression of this pregnancies were divided into: particular situations (gemellary pregnancy 21%, in vitro fertilization 8%); abnormal pregnancy (placenta praevia 8%, oligo and polyhydramnios 5%, gestational diabetes 5%, pre-eclampsia 31%); incidents during pregnancy (imminent abortion, abdominal pains and bleeding 32%). We note that 204 of the deliveries were spontaneous and that 62 were C-sections. 84,96% (226) of the deliveries were on due date whereas 40 were preterm deliveries.

The most frequently encountered types of CHD are listed in Table 1. The most frequent CHD was atrial septum defect (ASD) present in 29,69% of patients while transposition of the great vessels was present in 1,87% of children. 33,08% of patients with confirmed CHD suffer from complex heart defects. The most frequent association is the one between bicuspid aortic valve and stenosis or aortic regurgitation (12 patients, 13,63%), followed by the atrial septal defect — patent ductus arteriosus (9 patients, 10,22%) and the ventricular septal defect — tricuspidic regurgitation associations 9 patients, 10,22%). Eight patients (9,09%) suffer from the tetralogy of Fallot — atresia/hypoplasia of the pulmonary artery association. The rarest association is the one between ventricular septal defect and coarctation of the aorta, association encountered in only 1 patient.

87,60% (233) patients included in the group under study do not suffer from chromosome abnormalities, whereas 12,40% (33) of these patients do suffer from this type of pathology. The highest incidence (78,78%) is recorded for Down syndrome, which affects 26 children, followed by Turner syndrome.

The most frequent postnatal complication in CHD patients was cardiomegaly, followed by pulmonary hypertension (Figure 1).

29,94% of the patients underwent corrective surgery, the rest remained on medication. The highest incidence rate is recorded for tetralogy of Fallot (42,85%), followed by atrial septal defect and ventricular septal defect

(37,68%), the coarctation of the aorta 12,98% and transposition of the great vessels (6,49%).

The highest number of surgeries was performed on toddlers, preschoolers and infants. The fewest surgeries were recorded children having reached puberty (Figure 2).

On average, tetralogy of Fallot cases were operated on 16,6 months after diagnosis. This condition is followed by the atrial septal defect (10,5 months), ventricular atrial defect (10 months), common atrioventricular canal (6 months), patent ductus arteriosus (4 months) and transposition of the great vessels (2,5 months).

Discussion

We determined the beginning and the incidence of the pathology, as well as its association with other syndromes and defects. We analyzed symptomatology and gathered data on the age at which the congenital heart defects were diagnosed, as well as other data regarding the optimal age for performing surgical treatment, therapeutic attitude and results obtained.

Over the decades the prevalence of CHD birth increased substantially, from 1 per 1,000 live births in 1930 to 9 per 1,000 live births in recent years [7]. The rise in observed prevalence of CHD is likely multifactorial. This may be caused by changes in diagnostic methods and screening modalities rather than a true increase. Specialized pediatric cardiologists are being trained and the screening for CHD became an important step before noncardiac surgery causing an increase in diagnoses of minor lesions such as a small ventricular septum defect (VSD) or ASD. Survival of premature infants has improved over the last century, attributing to an increase in total CHD and especially VSD birth prevalence [6].

In addition, the patient population with GUCH is steadily increasing and their offspring is at increased risk of having a congenital abnormality [8]. Furthermore, factors such as maternal pre-gestational diabetes mellitus, phenylketonuria, infections, various therapeutic drug exposures, vitamin A use, have been proven to be associated with increased risk of CHD [9]. The impact of increased use of fetal echocardiography and pregnancy termination on reduction of CHD birth prevalence is expected in the next time periods [10].

One reason could be that the classification of CHDs is challenging because of the wide range of known defects, with different underlying etiologies for each class of defects.

Congenital heart defects include a range of defects that, according to errors in specific sequences of cardiac development can be broadly be classified [11]. Various heart malformations may occur in combination or, as single defects. However, an increase in prevalence due to improved diagnostics may also have been counteracted by increased prenatal screening for congenital malformations and subsequent termination of affected pregnancies. In the present study, the prevalence of severe CHDs overall and by specific defect corresponded well with estimates from comparable population-based registers [12].

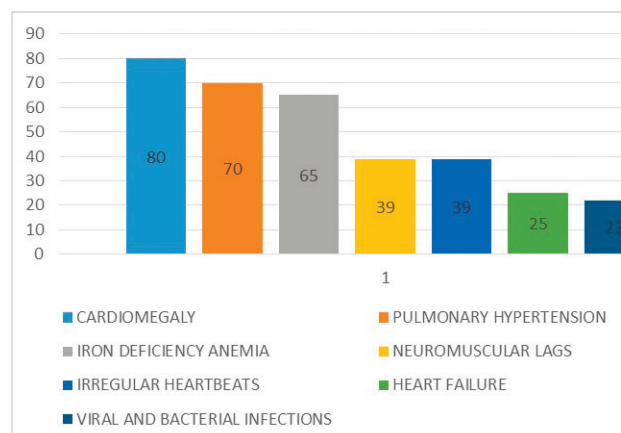


Fig. 1. The histogram showing the postnatal complications in CHD patients.

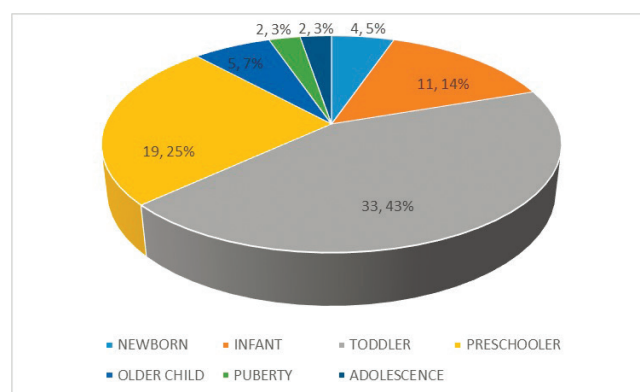


Fig. 2. The scatter-plot showing the age groups.

For some time, the pathogenesis of CHD has been attributed to genetic and environmental factors, including possible interactions between them. The epidemiological evidence strongly points to genetic factors playing a crucial role in the pathogenesis of CHD. The causes of CHD remain largely unknown. Aneuploidies such as trisomy 21 (causing Down syndrome) are strongly associated with CHD. Using technologies that detect copy number variants has uncovered numerous other segmental aneuploidies that cause CHD [13]. However, genetic factors underlying CHD largely remain to be elucidated. This is due to the challenges associated with that pathology.

The increasing prevalence of CHDs reported was confirmed in the present study. This is mostly due to an increasing number of isolated septal defects diagnosed in infancy, although we also found that severe defects contributed to the increase in CHD prevalence. It remains uncertain whether detected differences in CHD birth prevalence represent true or merely methodological differences.

In the future, the etiology of CHD needs to be further clarified and population wide prospective birth defect registries covering the entire world population are needed to determine the exact birth prevalence. These data have been important in generating interest in adult CHD as a new subspecialty of cardiology.

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IN VITRO SIMULATION RESEARCH ON THE HOOP STRESS OF MYOCARDIAL BRIDGE — CORONARY ARTERY

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An analog device which can simulate myocardium bridge oppresses mural coronary artery is designed. The device can be used to research the dynamic changes of the proximal and distal hoop stresses. Meanwhile, the independent regulation of the hoop stresses is realized. The "myocardial bridge — coronary artery" analog device is built to adjust the external pressure of the simulated coronary artery and the oppression level of the myocardial bridge and to record the changes of the hoop stresses. The In vitro simulation experiment indicate that the anomaly of hoop stress mainly occurs in the proximal end. As the oppression level increases, the mean proximal hoop stress and the oscillatory value (maximum-minimum) increase obviously. The "myocardial bridge — coronary artery" analog device can provide a method to study the influence of the hoop stress on the mural coronary artery in vitro.

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Key words: mural coronary artery, myocardial bridge, hemodynamic, hoop stress.

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IN VITRO ИМИТИРУЮЩЕЕ ИССЛЕДОВАНИЕ КОЛЬЦЕВОГО НАПРЯЖЕНИЯ МИОКАРДИАЛЬНОГО МОСТА — КОРОНАРНОЙ АРТЕРИИ

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Предложено аналоговое устройство, которое может имитировать угнетение миокардиальным мостом стенки коронарной артерии. Устройство может быть использовано для исследования динамических изменений проксимального и дистального кольцевых напряжений. Между тем, реализуется независимое регулирование кольцевых напряжений. "Миокардиальный мост — коронарная артерия" аналоговое устройство создано для регулировки внешнего давления смоделированной коронарной артерии и угнетения уровня миокардиального моста и для записи изменений кольцевых напряжений. In vitro имитационного эксперимент указывают на то, что аномалия кольцевых стресс возникает в основном в проксимальном конце. По мере того, как уровень угнетения повышается, среднее проксимальное кольцевое напряжение и колебательного значение (максимум-минимум), соответственно, увеличивается. "Миокардиальный мост — коронарная артерия" аналоговое устройство может

обеспечить метод для изучения влияния кольцевого напряжения на стенки коронарной артерии in vitro.

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Ключевые слова: стенка коронарной артерии, миокардиальный мост, гемодинамика, кольцевое напряжение.

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Introduction

The normal coronary artery and its branches are usually located under the epicardium. When a section of the coronary artery covered by the superficial myocardium is located in the myocardium, the coronary artery is called mural coronary artery (MC) and the myocardium is called myocardial bridge (MB).

A patient needs treatment when MC stenosis is over 50%. Sometimes the effect of drug therapy is poor for some MB patients and a part of MB patients even cannot tolerate drug therapy, so percutaneous transluminal coronary angioplasty or stent implantation is usually used for them. Coronary artery stent implantation not only can correct the abnormal MC hemodynamic, but also can make the MC blood flow return to normal. However, 10% — 50% of the patients may develop stent restenosis after receiving coronary artery stent implantation and even more seriously, the coronary artery rupture may happen in or after the treatment [1–3].

The hoop stress is one of the important hemodynamic factors. It is the stress along the tangential direction of the artery wall's cross section and it is mainly related to the vascular rupture [4–5]. Therefore, the research on MC hoop stress distribution can help us to prevent the coronary artery rupture in or after stent implantation.

Now, there are some researches on the numerical simulation of the normal artery wall residual strain and stress [6–8].

The strain cavity system can provide tensile stress environment [9], so the normal blood vessels under hoop stress can be simulated in vitro. However, the strain cavity system cannot simulate the hoop stress environment when the MB exists around the coronary artery. So a new device is needed. It should be able to simulate the MB oppressing the coronary artery, acquire the parameters related to the hoop stress, and have durable, repeatable and controllable experimental conditions.

Methods

1. The structure and function of the device

Figure 1 is the block diagram of the “myocardial bridge — coronary artery” analog device structure. The air compressor can inflate and the gas moves into the gasholder to make the pressure stable. The pressure sensor is set at the top of the gasholder to measure the internal pressure. Then the gas flows through proportional pressure valve, and eventually enters into the closed 3-D flow control chamber, so it can provide external pressure for tubular elastic cavity, change the external wall pressure, and regulate the hoop stress. When the internal pressure of the gasholder rises to 30kPa, the air compressor will stop inflating. When the internal pressure of the 3-D flow control chamber is lower than the set value, the gas stored in gasholder will keep on entering into the 3-D flow control chamber through the proportional pressure valve. When the internal pressure of the 3-D flow control chamber is higher than the set value, the gasholder will stop supplying the gas and the proportional pressure valve will be opened to release the gas so as to realize the decompression. The drive motor can drive the MB blocks to oppress the tubular elastic cavity.

Figure 2 is the map of the 3-D flow control chamber. The chamber is a closed organic glass cube and the internal situation can be observed clearly. The size of the internal chamber is 125mm×110mm×55mm (length×width×height). The volume of the 3-D flow control chamber is much larger than that of the simulated coronary artery. The device can simulate the coronary artery with 4~5mm inner diameter and 80mm length. Measuring point 1 is set at the position where the fluid flows in order to measure the proximal pressure while measuring point 2 is set at the position where the fluid flows out to measure the distal pressure. The MB blocks are set at the both radial sides of the simulated MC. The blocks, which are driven by a motor, conduct the straight reciprocating motion along the guide rail according to the preset depth to oppress the simulated MC. Bilateral or unilateral compression and different sizes' blocks can be chosen to meet the experimental requirement.

2. Theoretical basis

The hoop stress of the circular tube can be obtained through the following equation [10]:

$$\sigma_{\theta} = \frac{\frac{r_0^2}{r_i^2} + 1}{\frac{r_0^2}{r_i^2} - 1} q_1 - \frac{1 + \frac{r_i^2}{r_0^2}}{1 - \frac{r_i^2}{r_0^2}} q_2 \quad (1)$$

where σ_{θ} is the hoop stress of the wall, q_1 is the internal wall pressure, q_2 is the external wall pressure, r_0 is the external radius under the load, r_i is the internal radius under the load, and r is the radius at any place under the load.

To calculate the internal wall hoop stress, we set r to be r_i . In real, the radius r_0 and r_i of the elastic tube are

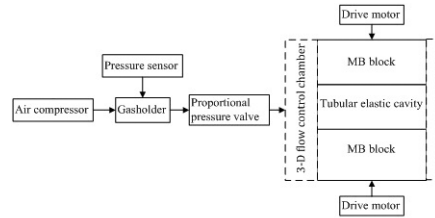


Fig. 1. Block diagram of the “myocardial bridge- coronary artery” analog device structure.

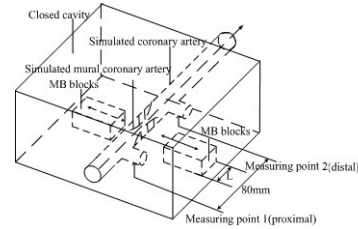


Fig. 2. The map of three-dimensional flow control chamber.

influenced by the pressure wave. Therefore, to obtain the geometrical and mechanical characteristics of the silicone tube flow chamber under the impulse, we use the pressure sensor and the parallel light camera to measure the pressure wave and the external radius wave of the silicone tube flow chamber, respectively. By fitting the pressure wave and the external radius wave, we find that the external radius is the monotone function of pressure,

$$d = a + b \times p + c \times p^2 - d \times p^3 + e \times p^4 \quad (2)$$

where d is the external diameter of the silicone tube under the load, p is the pressure of the silicone tube flow chamber, and the other parameters are

$$a \ 4.91 \ b \ 3.17 \times 10^{-3} \ c \ 1.18 \times 10^{-5} \ d \ 4.81 \times 10^{-7} \ e \ 2.39 \times 10^{-9}$$

Denote the internal and external radii of the silicone tube under the load by $r_i(t)$ and $r_0(t)$. Denote the initial internal and external radii of the tube by R_0 and R_i . Due to the incompressible characteristic of the silicone tube [11], we have

$$\lambda_z \pi (r_0^2(t) - r_i^2(t)) = \pi (R_0^2 - R_i^2) \quad (3)$$

Thus, the relationship between the internal and external radii of the tube under the load is

$$r_i(t) = f(r_0(t)) = \sqrt{r_0^2(t) - \frac{1}{\lambda_z} (R_0^2 - R_i^2)} \quad (4)$$

Since the longitudinal stretch ratio $\lambda_z = 1.2$ $R_0 = 2.465$ mm $R_i = 2.165$ mm we have

$$r_i(t) = f(r_0(t)) = \sqrt{r_0^2(t) - \frac{1}{1.2} (2.465^2 - 2.165^2)} = \sqrt{r_0^2(t) - 1.1575} \quad (5)$$

Then, the hoop stress of the silicone tube flow chamber system under the impulse can be calculated by

$$\sigma_{\theta} = \frac{2r_0^2 - 1.1575}{1.1575} q_1 - \frac{2r_0^2}{1.1575} q_2 \quad (6)$$

3. Experimental design

According to the clinical parameters of normal human [12], we set that the systolic blood pressure of coronary artery is 120 mmHg, the diastolic pressure is 80 mmHg, the mean flux is 205 mL/min, and the heart rate is 60 min⁻¹. During systole, the myocardial bridge oppresses the mural coronary artery [13–16]. Therefore, in the experiment, the systole has the same frequency with that MB oppresses MC, and the maximal output pressure and the maximal deflection of MB keep synchronous. The fluid in the tube is a mixture of low molecular dextran and normal saline with a ratio of 3:1, whose viscosity is 3.8×10^{-3} Pa·S [17].

1) Contrast the MC proximal and distal pressure waves of clinical MB patients with the results of the analog device; 2) In the case that the external pressure of coronary artery is constant, change the press situation to observe the changes in the proximal and distal hoop stress; 3) Remove the oppression of MB, and change the external pressure of the tube to observe the changes in the proximal and distal hoop stress.

Results

1. Pressure wave

Figure 3 shows the pressure wave of coronary artery in human body [18]. Figure 4 shows the pressure wave of the analog device when the level that MB oppresses MC is 100%. It is seen from the two figures that the simulation result have the same characteristic with that in human body, which is called “water hammer” [19].

2. Proximal and distal hoop stress when MB oppresses MC

Under normal atmospheric pressure, the MB oppresses MC on different levels. Based on the measured data, the curves of the mean proximal and distal hoop stresses with different oppression levels are shown in Figure 5. As the oppression level increases, the mean proximal hoop stress increases significantly, while the mean distal hoop stress remains unchanged. The oscillatory value of the proximal hoop stress (maximum-minimum) is obviously higher than that of the distal hoop stress. Moreover, an increase in oppression level leads to an increase in the oscillatory value of proximal hoop stress. (Figure 6)

3. Independent regulation of hoop stress

The hoop stresses changing with external pressure of simulated mural coronary artery are shown in Figure 7. The analog device can maintain constant internal pressure q_1 , flux, and other parameters. Change the external pressure q_2 to adjust the value of internal hoop stress. The larger q_2 is, the less the hoop stress is.

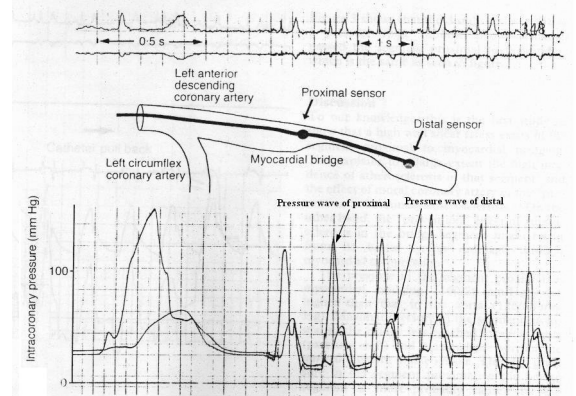


Fig. 3. The proximal and distal pressure wave of mural coronary artery in human body.

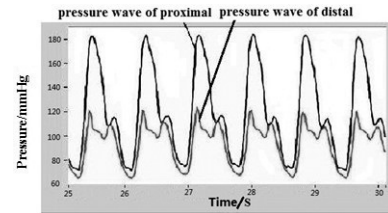


Fig. 4. The proximal and distal pressure wave of mural coronary artery in the analog device.

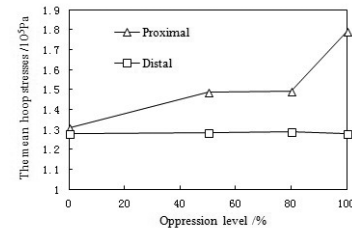


Fig. 5. The mean hoop stresses of the simulated mural coronary artery.

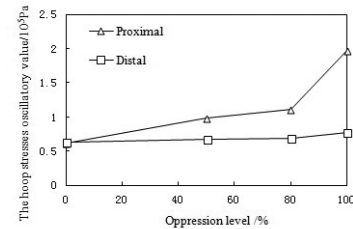


Fig. 6. The hoop stresses oscillatory value of the simulated mural coronary artery.

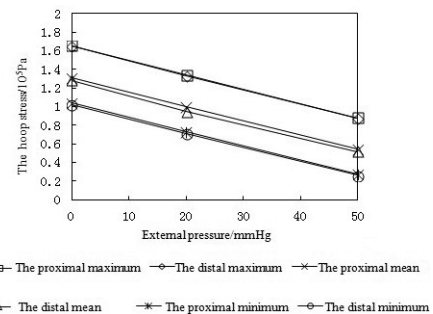


Fig. 7. The hoop stresses changing with external pressure of the simulated mural coronary artery.

Conclusions and discussion

Hoop stress plays an important role in the process of the reconstruction of the blood vessels. However, most hemodynamic researches focus on the shear stress at home and abroad nowadays. The reports about the researches on hoop stress are relatively less.

The influence of the abnormal MC proximal hoop stress caused by MB on the coronary artery disease has not been reported and the influence of MB on the effect of interventional therapy with severe atherosclerosis at proximal MB is not clear [20–22].

The physiological parameters such as blood pressure and blood flow relate to the myocardial bridge coronary artery. It is hard to study the clinical symptoms which caused by a single specific hemodynamic parameter.

In fact, we simulate four situations that MB oppresses MC. The oppression levels are 0%, 50%, 80%, and 100%, respectively. As the oppression level increases, the proximal pressure increases gradually, and the distal pressure remains unchanged. The most representative result, i.e., the pressure wave of the 100% oppression level is shown in this paper. Hypertension and atherosclerosis have reciprocal causation [23–25]. As a result, the increase in the proximal blood pressure caused by MB is closely related with atherosclerotic lesions.

The device in this paper simulates and calculates the proximal and distal hoop stresses of MC. The results indicate that the proximal pressure is much higher than the distal pressure. As a result, the anomaly of hoop stress mainly occurs in the proximal end. As the oppression level

increases, the mean proximal hoop stress and the oscillatory value (maximum-minimum) increase. The increase in the mean value results in higher risk of the proximal MC rupture. Meanwhile, as the oscillatory value increases, the proximal end is in the long fatigue load situation, which increases the probability of the rupture.

According to Eq. (6), the proximal and distal hoop stresses are only the functions of the internal pressure q_1 and the external pressure q_2 . Therefore, we set q_1 to be constant and change q_2 to adjust the value of hoop stress. The main aim of this device is not to simulate a particular clinical disease, but to provide an experimental environment, in which the blood pressure, the blood flux, the heart rate, and other physiological parameters are set, and the changes of hoop stress of MB are discussed. Whether the change of the external pressure occurs or not in clinic has not been reported yet.

The increase in the proximal pressure in MC caused by MB is closely related to the formation of atherosclerosis. The higher mean hoop stress and oscillatory value increase the risk of the blood vascular rupture. The simulation device can provide a method to study the hoop stress of MC in vitro. In this paper, when MB presses MC, the changes of internal radii of proximal and distal end are small, which can be ignored. Therefore, we use Eq. (6) to calculate the hoop stress approximately. However, when the internal radii suffer large deformation, Eq. (6) cannot be used to calculate the hoop stress. The method to obtain the hoop stress of MC in this situation will be studied in the future work.

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THE LIST OF MATERIALS PUBLISHED IN THE RUSSIAN JOURNAL OF CARDIOLOGY, 2014, 4 (108) – 7 (111)

CLINICAL GUIDELINES

2013 ESC GUIDELINES ON CARDIAC PACING AND CARDIAC RESYNCHRONIZATION THERAPY

The Task Force on cardiac pacing and resynchronization therapy of the European Society of Cardiology (ESC). Developed in collaboration with the European Heart Rhythm Association (EHRA).

Russ J Cardiol 2014, 4 (108): 5–63

2013 ESC GUIDELINES ON THE MANAGEMENT OF STABLE CORONARY ARTERY DISEASE

The Task Force on the management of stable coronary artery disease of the European Society of Cardiology

Russ J Cardiol 2014, 7 (111): 7–79

MYOCARDITISES, VALVULAR AND NONCORONAROGENIC DISEASES

THE BLOOD FLOWS IN THE LEFT VENTRICLE AS PREDICTORS FOR MYOCARDIAL DYSFUNCTION IN DILATED CARDIOMYOPATHY

Sandrikov V. A.¹, Kulagina T. Yu.¹, Krylov A. S.², Yatchenko A. M.²

Abstract

Aim. To evaluate the treatment results and to estimate the early predictors for myocardial dysfunction in patients with DCMP.

Material and methods. Totally 69 patients with DCMP (median age 42±14) were investigated before and after operation. Patients were divided into 3 groups: 1st — 69 patients before surgical treatment; 2nd — 41 patients those who were examined in 9–12 months after operation; 3rd — patients being monitored for more than 24 months after operation. The control consisted of 110 volunteers with the median age 37±8 y. o. To all patients the echocardiography was applied using expert class Vivid E9 (GE, USA) machine with multifrequency sensor 3,5–5,0 MHz. To visualize flows in the left ventricle the flow velocity was registered in the areas of fiber ring, middle and apical areas.

Results. With the LV function disturbing in DCMP patients the rise of pre- and postload causes significant changes in myocardial functioning. The direction of blood flow in the LV significantly changes with hypertrophy of myocardium and papillary muscles, valve dysfunction and other disorders. We had concluded that in DCMP, at the same time with high EDV and ESV there is incessance of blood flow which determines heart work by continuous blood motion, elasticity of magistral vessels and myocardium contraction. By echocardiography and computed tomography it was found that heart rotation is in order from the right to the left segments of basal area and then to descending and ascending segments of the heart apex.

Conclusion. The velocity of myocardial shifts, of blood flows in the LV make possible to evaluate heart functioning in patients with heart failure and to estimate the effectiveness of surgical treatment in closer and further postoperational periods. Basing on the measurements of blood flows in heart chambers and on estimation of intraventricular pressure gradients (from the apex to basement) it is possible to analyse the functioning and the performance of valves in patients with DCMP. The appearance in LV of additional turbulent flows, the decrease of flow velocity during the cardiac contraction cycle in one or another part are responsible for the failure and can be regarded as early predictors of myocardial dysfunction.

Russ J Cardiol 2014, 5 (109): 7–12

Key words: echocardiography, flows in the left ventricle.

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CONTEMPORARY MASKS OF THE MYOCARDITIS (FROM CLINICAL SIGNS TO DIAGNOSIS)

Blagova O. V., Nedostup A. V.

Abstract

Contemporary myocarditis classifications are usually made up by morphological criteria due to a critical role of biopsy in its diagnostic. However in general medical practice this method is quite rare, though in the real practice internists and cardiologists meet this disease more and more often, including its non-classical forms. Clear connection of cardiac symptomathic with an infection is the most specific sign of myocarditis, though its absence does not rule out the diagnosis. Using biopsy and complex algorithm of diagnostics developed on the basis of biopsy we have usually seen these types: 1. Latent (without decompensation and general inflammatory changes) myocarditis in patients with so-called idiopathic rhythm and conduction disorders including atrial fibrillation; 2. Various clinical course and immunity-involvement types in patients with the dilated cardiomyopathy; 3. Paraneoplastic myocarditis; 4. Myocarditis with infarction-like manifesting (as acute and benevolent in its course and prognosis, as chronic with the outcome into severe heart failure), microvascular angina, and combination of myocarditis with coronary atherosclerosis and real MI; 5. Myocarditis in patients with different genetic cardiomyopathies (including arrhythmogenic right ventricle dysplasia and noncompact myocardium); 6. Myocarditis as the sign of latent autoimmunity disorders. The complete list and analysis of clinical situations is provided, in those it is obligatory to confirm or rule out a myocarditis. The guidelines for differential diagnosis are given with the discussion of various pathogenetic mechanisms clarification of which makes possible a basis therapy.

Russ J Cardiol 2014, 5 (109): 13–22

Key words: myocarditis, idiopathic arrhythmias, dilated cardiomyopathy, infarctionlike type, microvascular angina, endomyocardial biopsy.

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THE SIGNIFICANCE OF FUNCTIONAL AND ETHIOLOGICAL DIAGNOSTIC FOR TREATMENT STRATEGY DECISION IN PATIENTS WITH DILATED CARDIOMYOPATHY

Frolova Yu.V.

Abstract

Aim. To evaluate the role and importance of the functional and etiological diagnosis in determining the surgical treatment of patients with dilated cardiomyopathy (DCM).

Material and methods. We examined 156 patients (40 women and 116 men) with dilated cardiomyopathy (DCM) aged 18–75 (average age — 48.8±/– 11.4) for the period from 2008 to 2013. The history of the disease averaging 54.8 ±/– 5.7 months; 15 (10%) of patients were in functional class II, 49 (31%) — in class III, 92 (59%) — in class IV.

Results. The mean end-diastolic LV diameter was 7.45±/– 1.2 cm, ejection fraction — 26.7±/– 2.1%. We performed blood PCR analysis in all the patients: Genome of herpes simplex virus type 1 was reported in 14 (9%), type 2 — in 7 (4%), type 6 — in 12 (8%) patients; of cytomegalovirus — in 20 (13%), of Epstein-Barr virus — in 24 (15%), of parvovirus B19 — in 29 (19%); we performed morphological study of the myocardium to detect cardiotropic viruses genome in 66 patients: genome of herpes simplex virus type 6 was found in 13 (23%), of cytomegalovirus — in 7 (12%), of Epstein-Barr virus — in 9 (15%), of parvovirus B19 — in 24 (42%). Depending on etiological factors, initial functional state of the patient as well as the severity of valvular regurgitation and the degree of interventricular dyssynchrony, 24 patients were implanted with cardioverter defibrillator (ICD) and 38 patients — with cardiac resynchronization therapy with cardioverter defibrillator function (CRT-D): in total, 62 patients with DCM; 24 patients underwent organ conserving reverse cardiac remodeling; orthotopic heart transplantation was performed in 13 patients; conservative treatment group consisted of 57 patients with DCM for whom surgical treatment was not recommended or impossible at the moment of the examination.

Conclusion. These data indicate that application of complex etiological and functional diagnostics allows us not only to make nosological diagnosis of patients with DCM but also to determine the type of treatment and prognosis.

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Key words: dilated cardiomyopathy (DCM), heart failure, reverse remodeling of the heart, endomyocardial biopsy, cardioverter-defibrillator (ICD), resynchronization therapy (CRT-D).

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DIFFERENTIAL DIAGNOSIS OF HYPERTROPHIC CARDIOMYOPATHY AND HYPERTENSIVE HEART DISEASE BY EXERCISE TESTING

Krylova N.S., Krylov A.L., Poteshekina N.G.

Abstract

Aim. To assess the effectiveness of a bicycle ergometer exercise test in differentiation of hypertrophic cardiomyopathy (HCM) and hypertensive heart disease (HHD).

Material and methods. 42 patients with HCM (mean age 49,8±15,3–28 male) and 25 patients with HHD (mean age 47,0±12,4–16 male) were studied. All patients underwent upright bicycle ergometer exercise test after withdrawal of drug therapy.

Results. It is well-known that abnormal blood pressure response (ABPR) and ST depression with angina during exercise are the criteria for the termination of test (RTT) and are the HCM attributes (after ruling out the coronary atherosclerosis by coronarography). With the use of nonparametric statistics we found significant difference between HCM and HHD in systolic blood pressure (SBP) at the end of the test (174,6±30,8 and 210,4±21,1 mmHg; p=0,000006), time recovery after test (TR) (10,0±4,0 and 7,1±1,6 min; p=0,007), breathlessness as a RTT (38,4% and 4%, p=0,022); extrasystole as a RTT (12,5% and 0%). With the use of logistic regression we found a dependency for differential diagnosis of HCM and HHD: Diagnosis = 0,41*SBPe–40,79–3,65*TR–13,34*BR–41,87*EXT–1000*OTH Where SBPe is SBP at the end of the test; TR equals 1 if breathlessness was the RTT and 0 otherwise; EXT equals 1 if extrasystole was the RTT and 0 otherwise; OTH equals 1 if ABPR, ST depression or stenocardia were the RTT and 0 otherwise. Diagnosis is greater than 0 for HHD and less than 0 for HCM patients. For all patients included in our study the dependency provides correct result.

Conclusion. The exercise testing gives useful information and can be applied for differential diagnosis of HCM and HHD.

Russ J Cardiol 2014, 5 (109): 29–34

Key words: hypertrophic cardiomyopathy, hypertensive heart disease, exercise test, differential diagnosis.

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HYPERTROPHIC CARDIOMYOPATHY: GENETIC ALTERATIONS, PATHOGENESIS AND PATHOPHYSIOLOGY

Vatutin N. T.¹, Taradin G. G.¹, Maron M. S.²

Abstract

The review is dedicated to the description of genetic alterations, pathogenetic mechanisms and pathophysiology of hypertrophic cardiomyopathy, based on the analysis of current up to date information. A contemporary data is provided on the role a plenty discovered mutations of structural, contractile and regulatory sarcomere proteins in cardiomyopathy. The main hypotheses of pathogenetic processes are highlighted, especially the disordered calcium exchange. The importance of genetic testing of patients with hypertrophic cardiomyopathy and their relatives is underlined. The review concerns the basic pathophysiologic characteristics of the disease according to their diagnostic, clinical and prognostic value. Except the description of pathophysiologic properties, as a matter of fact, the obstruction of outflow in the left ventricle, diastolic dysfunction, myocardial ischemia and rhythm disorders, the connection of these conditions is underlined to clinical picture, and the role of contemporary instrumental diagnostic methods (positron-emission tomography, computed tomography) in early diagnostic and monitoring of the disease.

Russ J Cardiol 2014, 5 (109): 35–42

Key words: hypertrophic cardiomyopathy, genetic mutations, pathogenesis, pathophysiology

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CONTEMPORARY METHODS FOR MYOCARDIAL FUNCTION EVALUATION IN PATIENTS WITH HYPERTROPHIC CARDIOMYOPATHY BEFORE AND AFTER SURGICAL TREATMENT

Van E. Yu., Kulagina T. Yu., Berezina E. V., Frolova Yu.V., Abugov S. A., Dzemeshevitch S. L.

Abstract

Aim. To invent and qualify a diagnostic algorithm for systolic and diastolic myocardium function evaluation in the left ventricle in patients with hypertrophic cardiomyopathy before and after surgical treatment.

Material and methods. Totally 88 patients included, 54 with hypertrophic cardiomyopathy (27 male, 27 female) with median age 59 ± 13 y. o. Obstructive type of HCMP was found in 41 pt. Transluminal ethanol-based septal ablation was done for 17 pts. Myoectomy/myotomy was done for 11 pts. The control consisted of 34 healthy volunteers with medial age $36,7 \pm 8,3$ y. o.: 24 men (70%) and 10 women (30%). To everyone included the echocardiography was performed using the Vivid E9 machine (GE, USA) with multifrequent sensor 3,5–5,0 MHz. The data was then processed by computer-based Multivox program. The “flow-volume” loop of the single cardiac cycle was reconstructed using numeric data for everyone of patients; also the data on myocardium segment shift were used.

Results. The parameters of volume change rapidity ($dVol/dt$ (s, d)) and the parameters of systolic and diastolic summes of normal velocities (V (s, d)) serve as strict independent predictors of the impaired systolic and diastolic function of LV myocardium and also as early markers of LV disordered function recovery in HCMP after surgical treatment. The markers of long axis diastolic shift (dL/dt (d)) and diastolic volume changes ($dVol/dt$ (d)) are the most accurate in prediction of left ventricle changes after surgical treatment in HCMP.

Conclusion. We have invented a novel and original approach to the evaluation of systolic and diastolic myocardial function in patients with obstructive type hypertrophic cardiomyopathy before and after surgical treatment using our own algorithm based on echocardiographical measurements of myocardium shift rapidity.

Russ J Cardiol 2014, 5 (109): 43–48

Key words: echocardiography, hypertrophic cardiomyopathy, myocardium shift rapidity, myotomy, alcohol ablation.

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BICUSPID AORTIC VALVE (A DEVELOPMENT OF INSIGHT INTO VALVULOPATHIES)

Dzemeshevitch S. L., Ivanov V. A., Charchian E. R., Evseev E. P., Frolova Yu.V., Lugovoy A. N., Fedulova S. V., Khovrin V. V., Bukaeva A. A., Zaklyazminskaya E. V.

Abstract

Aim. To study different ways of development and combinational abilities of pathological changes common for bicuspid aortic valvulopathy.

Material and methods. Totally 207 patients included, who had during previous 5 years been operated for progression of inherited aortic valve defect. The age varied from 17 to 75 years (median $49,6 \pm 0,9$ y.), men to women — 3:1. Comorbidities included rheumatic fever in 33 (15,9%) patients and infectious endocarditis in the past in 45 (21,7%). In 111 (53,6%) patients aortic stenosis dominated and distension of ascending aorta — in 82 (39,6%) patients.

Results. For most of patients mechanical prostheses were used and only for 12 — biological; 13 patients underwent valvuloplastic or no any operation. One third of patients (31,9%) required a prosthesis of ascending aorta. Combinations of additional procedures (as aortic valve plastic or prosthesis, tricuspid plastic, left atrium plastic, septal defects sewing, coronary bypass grafting) were not unusual — in 57. In-hospital mortality reached 2,9%.

Conclusion. Bicuspid aortic valve is a specific kind of valvulopathy, commonly combined with aortopathy. The development of this pathology is probably inherited. Clinical picture of the defect develops during time and its exacerbation might be accelerated by rheumatic fever and infectious endocarditis. Surgical treatment is effective.

Russ J Cardiol 2014, 5 (109): 49–54

Key words: bicuspid aortic valve, aortopathy, valve prosthesis, the genetics of connective tissue dysplasia.

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NEONATAL MARFAN SYNDROME: CLINICAL DESCRIPTION AND COMPLEX APPROACH TO DIAGNOSTICS AND TREATMENT

Rumyantseva V. A., Rogozhina Yu. A., Kotlukova N. P., Zaklyazminskaya E. V.

Abstract

Aim. Molecular-genetic tests for neonatal type of Marfan syndrome make possible to clarify a diagnosis in children with multiple phenotype anomalies and to choose correct treatment strategy.

Material and methods. Medical-genetic testing and instrumental diagnostics (echo, Doppler, ECG, chest X-rays) made possible to guess the diagnosis of neonatal Marfan syndrome (MS). Direct DNA-diagnostics of MS for these patients including direct Sanger-sequencing of the coding plots and neighbouring intron areas of exons 24–32 gene FBN1 completely proved the diagnosis.

Results. First time in Russia in two non-relative families with newborns having multiple phenotype anomalies the diagnosis of MS was set at the first year of life and confirmed by molecular-genetic methods.

Conclusion. The results of the study must be introduced into practice at specialized pediatric, cardiological and cardiosurgical centres and departments to estimate the risk of sudden death, choose treatment strategy, prescribe gene-specific therapy.

Russian Journal of Cardiology 2014, 5 (109): 55–60

Key words: Marfan syndrome, fibrillin, DNA-diagnostics, genetic consulting in cardiology.

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ARRHYTHMOGENIC CARDIOMYOPATHY OF THE RIGHT VENTRICLE COMORBID WITH HEMODYNAMICALLY SIGNIFICANT SECONDARY INTERATRIAL SEPTAL DEFECT

Shapieva A. N., Zaklyazminskaya E. V., Frolova Yu. V., Nechaenko M. A., Shestak A. G., Dzemeshevich S. L.

Abstract

Congenital atrial septal defect (ASD) is a common heart defect. The subjects for differential diagnosis of atrial septal defect, also leading to morpho-functional disturbances in the right parts of the heart, must be either inherited or acquired diseases. One such disease is arrhythmogenic right ventricular cardiomyopathy (ARVC), which leads to higher risk of sudden cardiac death (SCD) in young people. In the article we present the case of the patient with congenital heart disease: atrial septal defect operated at the age of 19. Deterioration of the condition was interpreted as a consequence of atrial septal defect. During examination at Russian scientific centre of surgery named after B. V. Petrovsky an independent hereditary disease — ARVC was diagnosed. The disease was confirmed by molecular-genetic testing methods. A novel mutation in the gene p.S194L DSG2 homozygous was identified. On the basis of ARVC diagnosed on the basis of physical, instrumental and genetic testing, the decision was made to implant a dual-chamber frequency adaptive cardioverter-defibrillator (ICD) for the prevention of SCD risk. The further tactics of patient monitoring must include not only regular ECG, echocardiogram, ICD function testing, but also cascade screening mutations responsible for the development of the ARVC in family members.

Russ J Cardiol 2014, 5 (109): 61–65

Key words: ARVC, secondary ASD, ICD, genetic testing.

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THE CLINICAL POLYMORPHISM AND TREATMENT STRATEGY IN A LARGE FAMILY WITH BRUGADA SYNDROME

Saber S., Fazelifar A. F., Haghjoo M., Emkanjoo Z., Alizadeh A., Shojafard M., Dalili M., Houshmand M., Gavrilenko A. V., Zaklyazminskaya E. V.

Abstract

Brugada syndrome (BrS) is an inherited arrhythmia characterized by ST-segment elevation in V1-V2 leads followed by negative T-wave on standard ECG, and high risk of ventricular tachyarrhythmias and sudden cardiac death (SCD). A wide range of supraventricular arrhythmias and conduction disturbances was described for BrS. The disease was considered of the high frequency in Southeast Asia, but current estimation of BrS is at least 1:10 000 in all ethnic groups. At least 17 genes are known to be responsible for BrS. Approximately 15–30% of individuals with Brugada syndrome cases are affected by mutations in SCN5A gene. In this study we discuss the clinical polymorphism and surgical treatment in a large family with Brugada syndrome caused by p.A735V mutation in SCN5A gene.

Russ J Cardiol 2014, 5 (109): 66–71

Key words: Brugada syndrome, atrial fibrillation/flutter, sick sinus syndrome, SCN5A, implantable cardioverter-defibrillator (ICD).

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LIFE-THREATENING MANIFEST OF LONG-QT-SYNDROME

Polyak M. E., Podolyak D. G., Glazova O. V., Artyukhina E. A., Nechaenko M. A., Zaklyazminskaya E. V.

Abstract

Aim. To complete DNA-diagnostics for the patients with syncope and not showing clinically significant rhythm disorders, but with family anamnesis of sudden death.

Material and methods. Clinical case. The patient 22 y. o. consulted at RSCS n. a. Petrovsky with the primary diagnosis of "inherited epilepsy" and complaints on presyncope and dizziness. During examination there was no data found to prove the inherited epilepsy and clinically significant rhythm disorders. Taking into account the family anamnesis of sudden death a diagnosis of "idiopathic ventricular tachycardia" was suggested and the patient underwent two-chamber rate-adaptive cardioverter-defibrillator Maximo II DR D284DRG implantation. DNA-testing revealed a mutation of p.R583H in the gene KCNQ1, that had

been previously described as probable to cause type 1 long-QT-syndrome. During the next 12 month after implantation there were 2 proven strokes recorded. The patient was consulted by cardiologist to prescribe beta-blocker therapy.

Results. Although there were no clinically significant heart rhythm disorders found, the patient with suspected family type of idiopathic ventricular tachycardia underwent cardioverter-defibrillator setting up procedure. Molecular-genetic methods helped to prove the diagnosis of "long-QT-syndrome type 1" and the cascade family screening was started to choose a treatment strategy for asymptomatic mutation bearers.

Conclusion. By the example of the clinical case described we showed a significance of DNA-diagnostics in the diagnosis clarification, treatment strategy choice and sufficient medical-genetic consulting for the disease mentioned.

Russ J Cardiol 2014, 5 (109): 72–74

Key words: LQTS, KCNQ1, sudden cardiac death, idiopathic ventricular tachycardia.

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CARDIO-ONCOLOGY IN TREATMENT AND REHABILITATION PROGRAMS OF ONCOLOGICAL PATIENTS

Balluzek M. F., Ionova A. K.

Abstract

While studying the nearest and distant consequences of chemo- and radiation therapy, systemic effects of cancer on human, frequent comorbidity, a control of the state of cardiovascular system in all of the stages of medical cancer treatment become necessary. A classification of cardiological and cardiotoxic events, which are common in treatment of cancer, is provided. The need of development of the new interdisciplinary direction — cardio-oncology — in algorithm of treatment and rehabilitation process is revealed.

Russ J Cardiol 2014, 5 (109): 75–80

Key words: cardioncology, cardiotoxicity, cancer disease, cardiological rehabilitation of cancer patients.

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DIAGNOSTIC AND SURGICAL TACTICS IN PSEUDOTUMOROUS VOLUMINOUS HEART FORMATIONS

Nechaenko M. A., Kuznetsova L. M., Podolyak D. G., Kiprensky A. Yu.

Abstract

Aim. To study clinical and diagnostic, surgical and morphological properties of pseudotumorous heart formations, possibilities for early diagnostics and to invent optimal treatment strategy.

Material and methods. Petrovsky Centre for Surgery has the heart tumours treatment experience of 326 patients during the time from December 1962 till December 2010. Morphologically confirmed were tumours of 259 (79,4%) patients. At the current moment the study includes 67 patients with pseudotumorous formations of the heart, continuously supervised at the Centre from February 1960 till December 2010. Of those 36 were males and 31 females at the age of 2,2–74 (median 34,1±2,1),

Results. Total survival not including in-hospital mortality, evaluated by Kaplan-Meier method, gained 100% and 94,3% at the 1st and 24th year of observation, respectively. Analysis of the "life quality" of these patients at the remote periods after operation shows its significant improvement. Treatment results claimed as "good" were set for 62,8%; "satisfactory" for 31,4% and "nonsatisfactory" for 5,8% of cases. Treatment strategy for the patients with morphologically not confirmed voluminous formations (29,9%) was predestinated by smaller sizes (4–10 mm diameter), nonmobility that could be regarded as the risk for embolism, smooth echogenicity with sharp border, absence of hemodynamical malfunction and clinical signs.

Conclusion. The analysis has shown that on-time diagnostics of voluminous formations of the heart with pseudotumorous and morphologically non-recognizable properties is very complicated. Clinical awareness while interpreting the short clinical anamnesis and specificities of clinical picture made it possible to realise the individualized choice for the algorithm of further diagnostics taking into account an oncological determinancy. The success of the operations was predicted by the conditions of normo- or hypothermic perfusion and cold-pharmacological cardioplegy, ensuring optimal exposition and adequate protection for the myocardium, following the rules for prophylaxy of "tumours" fragmentation and embolism, and correction of comorbid valve pathology, inherited valve defects and ischemic heart disease.

Russ J Cardiol 2014, 5 (109): 81–87

Key words: pseudotumorous heart formations, echocardiography, surgical tactics.

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A CLINICAL CASE: A GIANT MYXOMA OF THE LEFT ATRIUM

Shilenko A. N., Bachinskaya I. N., Mataev V. S., Urvantseva I. A.

Russ J Cardiol 2014, 5 (109): 88–89

Key words: myxoma, left atrium.

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A LEFT ATRIAL GIGANTIC MIXOMA ON BACKGROUND OF MITRAL VALVE DYSPLASIA

Dzemeshevitch S. L., Frolova Yu. V., Rizun L. I., Dzemeshevitch A. S., Raskin V. V., Fedulova S. V., Dzeranova A. N., Mironovich S. A.

Abstract

Aim. To demonstrate a clinical case of mixoma with mitral regurgitation

Material and methods. The operation performed: excision of voluminous formation of the left atrium, mitral valve plastic with supporting ring Edwards Lifescience 32, interatrial septum plastic with the VASCUTEC patch under conditions of artificial circulation and pharmacy-cold cardioplegy.

Results. Complete myxoma excision, absence of mitral regurgitation after operation.

Conclusion. Complete myxoma excision and mitral regurgitation correction lead to a good clinical result.

Russ J Cardiol 2014, 5 (109): 90–92

Key words: cardiac myxoma, left atrium, mitral regurgitation, dysplasia.

FSBI Petrovsky Russian Scientific Centre for Surgery of the Academy of Medical Sciences, Moscow, Russia.

A 24-YEAR LASTING MONITORING OF THE FEMALE PATIENT AFTER ORTHOTOPIC HEART TRANSPLANTATION

Frolova Yu. V., Voronina T. S., Tsyplenkova V. G.

Russ J Cardiol 2014, 5 (109): 93–96

Key words: heart transplantation, immunosuppression.

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ORIGINAL ARTICLES

POLYMORPHISM OF PREDISPOSITION GENES IN CHRONIC OBSTRUCTIVE PULMONARY DISEASE AND ARTERIAL HYPERTENSION IN GERIATRIC PATIENTS

Shpagina L. A.¹, Voevoda M. I.³, Maximov V. N.³, Pospelova T. I.¹, Shpagin I. S.¹, Gerasimenko O. N.^{1,2}, Panacheva L. A.¹, Alicheva Ya. M.^{1,2}

Abstract

Aim. To assess the associations between predisposition genes (TGF- β 1, HHIP, IL6R, SOD3, and CHRNA3), in relation to peripheral vascular structure and function, endothelial dysfunction, and cytokine status, in geriatric patients with chronic obstructive pulmonary disease (COPD) and arterial hypertension (AH).

Material and methods. In total, 154 geriatric patients with either isolated AH or the combination of AH and COPD underwent clinical, functional, laboratory, ultrasound, and cytogenetic examination.

Results. The key associations between predisposition genes, in relation to peripheral vascular structure and function, endothelial dysfunction, and cytokine status, were identified in geriatric patients with COPD and AH who received short- or long-acting inhaled M-cholinolytics and steroids combined with perindopril monotherapy (10 mg/day; Prestarium, Servier Laboratories, France).

Conclusion. The combination of COPD and AH was characterised by significantly different distribution of genotypes and alleles (TGFB1 gene rs1804470 allele and HHIP gene rs1828591 allele), in relation to geriatric age. Patients with the COPD and AH combination had more severe endothelial dysfunction, cytokine activation, and disturbed structure and function of peripheral vessels (distal-proximal type). There were significant differences in peripheral vascular remodelling parameters among elderly vs. very elderly patients with COPD and AH.

Russ J Cardiol 2014, 4 (108): 65–74

Key words: mononucleotide genetic polymorphism, geriatric age, arterial hypertension, chronic obstructive pulmonary disease, vascular remodelling, endothelial dysfunction.

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MANAGEMENT OF IN-PATIENTS WITH UNCONTROLLED ARTERIAL HYPERTENSION

Logacheva I. V.¹, Safronova V. V.², Maximov N. I.¹, Baranova S. P.²

Abstract

Aim. To investigate the antihypertensive effectiveness of a fixed perindopril/amlodipine combination (Prestans) and its effects on the visit-to-visit variability of blood pressure levels and quality of life (QoL) among in-patients with uncontrolled arterial hypertension (AH).

Material and methods. The study included 35 patients (15 men and 20 women; mean age 50,4±8,9 years) who were hospitalised due to uncontrolled AH. The previously administered ineffective antihypertensive therapy was cancelled and replaced by Prestans (5/5, 10/5, 5/10, or 10/10 mg/day, subject to AH severity). The in-hospital monitoring lasted for 14 days and included daily assessment of office, systolic and diastolic BP (SBP, DBP), mean and pulse BP, intra-visit and visit-to-visit BP variability, and QoL (SF-36 questionnaire).

Results. All hospitalised patients had Stage III AH, including 31,4% with Degree 2 AH and 68,6% with Degree 3 AH. During the in-hospital course of Prestans treatment, the levels of SBP and DBP decreased from 184,2±14,6 to 142,1±13,8 mm Hg ($p<0,05$) and from 104,6±7,2 to 84,3±5,7 mm Hg ($p<0,05$), respectively. Mean and pulse BP levels also reduced significantly. The intra-visit variability of office SBP significantly decreased from Day 1 (5,07±0,9 mm Hg) to Day 14 (1,5±0,1 mm Hg; $p<0,05$). The visit-to-visit SBP variability also decreased, from 11,6±2,5 to 2,1±1,2 mm Hg, respectively ($p<0,01$). At baseline, the patients demonstrated a substantial reduction in both physical and mental health QoL parameters. The treatment was associated with a significant improvement in the psychological health domain (emotional and social functioning).

Conclusion. In patients with uncontrolled AH, the in-hospital treatment with Prestans resulted in a mean reduction of SBP/DBP levels by 38,4/19,6 mm Hg, a significant decrease in mean and pulse BP levels, and achievement of target BP levels in 82.9% of the patients as early as at Day 14 of the treatment. The amlodipine/perindopril treatment was also associated with reduced intra-visit and visit-to-visit BP variability, as well as with improved BP control, emotional status, and QoL.

Russ J Cardiol 2014, 4 (108): 75–81

Key words: perindopril/amlodipine, visit-to-visit variability, quality of life.

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IVABRADINE EFFECTIVENESS IN PATIENTS WITH CORONARY HEART DISEASE AND CHRONIC OBSTRUCTIVE PULMONARY DISEASE AFTER CORONARY ARTERY BYPASS GRAFT SURGERY

Kochetkova I. V., Minakov E. V., Streletskaia G. N.

Abstract

Aim. To study the anti-anginal effects of ivabradine in patients with effort angina and chronic obstructive pulmonary disease (COPD) after coronary artery bypass graft surgery (CABG).

Material and methods. In total, 120 men with Functional Class II–III stable effort angina, who underwent CABG approximately 3 years ago, underwent a complex examination using the devices “Eton” and “Holter-DMS”.

Results. Coraxan therapy was associated with a tendency towards reduced state index, decreased heart rate, and improved heart rate variability (HRV) parameters.

Conclusion. Coraxan (Servier Laboratories, France) can be recommended to patients with coronary heart disease and COPD after CABG, due to its anti-anginal effects as manifested in the reduced number of anginal attacks, improved quality of life, and improved HRV parameters.

Russ J Cardiol 2014, 4 (108): 82–85

Key words: Coraxan, chronic obstructive pulmonary disease, coronary artery bypass graft surgery.

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REDUCED RENAL GLOMERULAR FILTRATION AND SHORT- AND LONG-TERM PROGNOSIS IN PATIENTS AFTER CORONARY ARTERY BYPASS GRAFT SURGERY

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Abstract

Aim. To identify the risk factors and clinical features of acute kidney injury (AKI) in patients with chronic kidney disease (CKD) who underwent coronary artery bypass graft surgery (CABG); to assess the impact of reduced renal glomerular filtration on the short- and long-term prognosis in these patients.

Material and methods. The study included 487 patients (294 men and 193 women) aged 45–68 years (mean age 58,0±7,6 years), who underwent planned CABG. Before the intervention, CKD was registered in 330 patients (Group 1), while in 157 patients, no clinical,

laboratory, or instrumental evidence of CKD was observed (Group 2). AKI within the first 24 hours after CABG was diagnosed according to the RIFLE criteria (serum creatinine levels). The follow-up period was 3 years after CABG.

Results. In the early post-intervention period, Group 1 developed AKI significantly more often than Group 2: 59,4% vs. 25,1%, respectively ($p<0,001$). The main risk factors of AKI were arterial hypertension (AH), Type 2 diabetes mellitus, congestive chronic heart failure (CHF), and persistent atrial fibrillation for Group 1 and AH and congestive CHF for Group 2. Moreover, Group 1, in contrast to Group 2, was characterised by moderate and severe AKI, as well as by persistent and irreversible AKI. In-hospital lethality was higher for Group 1 than for Group 2 (16,1% vs. 6,0%, respectively; $p<0,001$), although this difference in AKI patients was not statistically significant (21,4% for Group 1 vs. 15,3% for Group 2; $p>0,05$). In patients with preexisting CKD (Group 1), 3-year survival was significantly lower than in Group 2 patients, irrespective of AKI development ($p<0,001$).

Conclusion. Reduced renal glomerular filtration affects both short- and long-term prognosis after CABG and increases the risk of AKI.

Russ J Cardiol 2014, 4 (108): 86–91

Key words: coronary artery bypass graft surgery, acute kidney injury, chronic kidney disease.

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TYPE D PERSONALITY AND QUALITY OF LIFE ONE YEAR AFTER CORONARY ARTERY BYPASS GRAFT SURGERY

Sumin A. N., Raikh A. N., Gaifullin R. A., Mos'kin M.G., Korok E. V., Bezdenezhnykh A. V., Ivanov S. V., Barbarash O. L.

Abstract

Aim. To investigate the effects of Type D personality traits on psychological status (PS) and quality of life (QoL) in patients with coronary heart disease one year after coronary artery bypass graft surgery (CABG).

Material and methods. PS was assessed at baseline and after CABG in 408 patients, who were divided into two groups: with Type D personality traits ($n=93$; Group 1) and without these traits ($n=315$; Group 2). The Spielberger-Khanin, depression, SF-36, and DS-14 scales were used for PS assessment.

Results. One year after CABG, fewer patients reported high levels of anxiety, and there was an improvement in physical functioning and physical status QoL domains ($p<0,05$). The percentage of patients with Type D personality traits did not change over time, suggesting that this chronic psychological risk factor is relatively stable. Type D personality traits negatively affected the levels of anxiety, depression, and QoL one year after CABG. According to the results of multivariate logistic regression analyses, type D personality and elevated levels of trait anxiety and depression independently predicted lower levels of psychological and physical QoL parameters.

Conclusion. The tendency towards psychological distress, a stable personality trait observed both before and one year after CABG, was associated with reduced psychological and physical QoL parameters. The pre-CABG assessment of personality traits could optimise the complex management strategy and improve QoL.

Russ J Cardiol 2014, 4 (108): 92–99

Key words: coronary artery bypass graft surgery, psychological distress, quality of life, Type D personality.

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EFFECTS OF RENAL ARTERY DENERVATION ON LEFT VENTRICULAR DEFORMATION AND BLOOD FLOW VELOCITY IN THE DISTAL SEGMENT OF ANTERIOR DESCENDING CORONARY ARTERY AMONG PATIENTS WITH RESISTANT ARTERIAL HYPERTENSION

Pavlukova E. N., Mordovin V. F., Pekarskiy V. V., Lichikaki V. A., Karpov R. S.

Abstract

Aim. To assess the dynamics of left ventricular (LV) longitudinal deformation and blood flow velocity in the distal segment of anterior descending coronary artery (ADCA) among patients with resistant arterial hypertension (AH) 12 months after renal artery denervation.

Material and methods. In seven patients with resistant AH (mean age $52,00\pm6,59$ years), bilateral renal artery denervation was performed. Five out of seven patients had concentric LV hypertrophy. The complex clinical and instrumental examination included the assessment of office and 24-hour blood pressure (BP) levels, echocardiography, speckle tracking imaging (2D strain), and transthoracic visualisation of the distal segment of ADCA.

Results. Twelve months after renal artery denervation, office BP levels decreased by 31/20 mm Hg. Mean 24-hour, mean daytime, and mean nighttime BP levels reduced by 15,58/14,62 mm Hg, 17,1/14,9 mm Hg, and by 21,1/14,47 mm Hg, respectively. There was an increase in global longitudinal LV deformation and local LV deformation (basal septal segment, basal and middle segments of anterior and posterior walls, and middle and apical segments of lateral wall). The improvement in longitudinal systolic LV function was associated with reduced linear velocity of diastolic blood flow in the distal ADCA segment, without similar systolic changes.

Conclusion. Our results suggest that renal artery denervation is linked to improved LV function; therefore, this method could be widely recommended for the management of patients with resistant AH.

Russ J Cardiol 2014, 4 (108): 100–107

Key words: resistant arterial hypertension, renal artery denervation, left ventricular deformation, speckle tracking imaging (2D strain), coronary blood flow.

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CAROTID ARTERY DUPLEX SCAN IN DIAGNOSING CORONARY ATHEROSCLEROSIS AND ASSESSING ITS SEVERITY

Gavrilova N. E., Meletskaya V. A., Yarovaya E. B., Boytsov S. A.

Abstract

Aim. To assess the role of carotid artery duplex scan in diagnosing coronary atherosclerosis of varied severity.

Material and methods. The study included 194 patients (126 men and 68 women) aged 33–85 years who were hospitalised to the State Research Centre for Preventive Medicine and underwent coronary artery angiography and carotid artery duplex scan. The severity of coronary atherosclerosis at coronary artery angiography was assessed by the Gensini score.

Results. The combination of carotid and coronary artery atherosclerosis was observed in 74,7% of the patients. Among those with carotid atherosclerosis, coronary atherosclerosis was registered in 92,4%. This suggests that carotid artery duplex scan is highly sensitive in diagnosing coronary atherosclerosis, despite its low specificity (27,0% patients without carotid atherosclerosis had coronary atherosclerosis). Positive predictive value (likelihood of disease in those with positive test results) of carotid artery duplex scan was 84%. Patients with carotid atherosclerotic plaques had significantly higher Gensini scores than patients with atherosclerosis-free carotid arteries (32 vs. 3,5, respectively; $p=0,012$), which suggests more severe coronary atherosclerosis in the presence of carotid atherosclerotic plaques. The intima-media thickness values over 0,9 mm were associated with higher Gensini scores (11 vs. 32,5, respectively; $p=0,003$), confirming more severe coronary atherosclerosis in these patients. Participants with severe coronary atherosclerosis had 3 or more carotid atherosclerotic plaques ($p<0,01$), typically of heterogeneous structure ($p=0,03$). The highest Gensini scores were observed in patients with atherosclerotic plaques in common carotid arteries.

Conclusion. The results obtained suggest that carotid artery duplex scan is highly informative in diagnosing coronary atherosclerosis and assessing its severity.

Russ J Cardiol 2014, 4 (108): 108–112

Key words: atherosclerosis, duplex scan, coronary artery angiography, carotid arteries, atherosclerotic plaques.

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EVALUATION OF PREGNANCY ASSOCIATED HYPERTENSIVE STATES

Shakhbasova N. A.

Abstract

Aim. The main aim of current study was to investigate the significance and prevalence of the different risk factors for hypertension, caused by pregnancy.

Material and methods. We evaluated different risk factors in 120 pregnant women with hypertensive states (main group) and in 50 healthy pregnant women at the same gestation period (control group). In pregnant women we evaluated the absence either presence of of pre-eclampsy risk factors: age, parity, hypertensive disorders during previous pregnancies, time gone since previous pregnancy, obesity, hypertension family anamnesis, infertility, multiple prencnacy, extragenital diseases. To calculate the relations between different qualitative signs the Pirson χ^2 used.

Results. During the study it was revealed that in hypertension disorders the women had one risk factor in 30 (35,5%), two risk factors in 29 (34,1%), three and more risk factors in 26 (30,6%). It was found that in 30% of pregnant with pre-eclampsy and gestational hypertension there are no any risk factors. Most significant risk factors were first pregnancy and extragenital pathology. Combination of three and more risk factors is an anamnestic marker for higher risk of severe pre-eclampsy.

Conclusion. The analysis of hypertension risk factors in pregnant women makes evidence-based the recognition of the high-risk group for pre-eclampsy. Further detailed diagnostic investigation of these women provides the opportunity to start a prophylaxy of hypertension disorders in pregnancy and to monitor the condition of clotting system, fetus condition and to improve the outcomes of a pregnancy. Absence of the risk factors does not decline a possibility of pre-eclampsy and requires the search for additional markers that would be early and pathogenetically proven signs.

Russ J Cardiol 2014, 5 (109): 97–100

Key words: pregnancy, gestational hypertension, pre-eclampsy, risk factors.

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SOCIO-ECONOMIC RISK FACTORS FOR CARDIOVASCULAR DEATH: DATA FROM 12-YEAR PROSPECTIVE EPIDEMIOLOGIC STUDY

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Abstract

Aim. Studying of the influence of socio-economic risk factors on relative risk (RR) of death from cardiovascular diseases (CVD) in non-organized population of Tyumen city.

Material and methods. The epidemiological study was performed with standard approaches on relevant selection of Tyumen citizens aged 25–64 y. During next 12 years the whole cohort (795 men, 814 women) was analyzed for the deaths from cardiovascular diseases (CVD). Multivariate regression model of proportional Kox risk used to estimate RR for cardiovascular death. RR with 95% CI calculated with added concomitant RF like: age, SBP and DBP, BMI, total cholesterol, triglycerides, HDL, smoking state, coronary heart disease anamnesis and arterial hypertension.

Results. By 12 years of observation there were 85 (10,7%) cases of cardiovascular death in men and 33 (4,1%) in women. Higher risk of cardiovascular death was in men with low educational level than in those with higher education (RR: 1,94, 95% CI 1,12–3,34). In women the same (RR: 3,42, 95% CI 1,53–7,64) in comparison to more educated women. After standartization of all concomitant factors the risk of cardiovascular death was significantly higher in men and women involved in hard physical labour (RR: 2,51, 95% CI 1,03–6,08 and 5,47, 95% CI 1,69–17,74, resp.), comparing to those of higher labour qualification (RR: 4,08 (95% CI 2,12–7,8), RR 3,19 (95% CI 1,22–8,34) and RR 3,18 (95% CI 1,90–5,34), resp. In women the relation was opposite: RR for cardiovascular death was higher for married women (3,21, 95% CI 1,28–8,06; $p < 0,001$), than for single.

Conclusion. The highest risk for cardiovascular death in non-organized Tyumen citizen cohort was found for those with lower educational level, involved into hard physical labour and single, divorced or widowed men. In women, opposite, being married was associated with higher risk of death from CVD.

Russ J Cardiol 2014, 6 (110): 7–11

Key words: social risk factors, cardiovascular death, prospective study.

¹Filial of FSBI SRI of Cardiology of Siberian Dept RAMS Tyumen Cardiological Centre, Tyumen; ²Interdepartmental Laboratory for Epidemiology of Cardiovascular Diseases of Siberian Dept of RAMS, Novosibirsk, Russia.

CLINICAL AND ECONOMIC EFFICACY OF PRIMARY PREDICTION ORGANISATIONAL MODEL FOR CARDIOVASCULAR DISEASES IN RAILWAY SYSTEM WORKERS

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Abstract

Aim. To study clinical and economic efficacy of the organisational model for primary prevention of CVD in men working at railway system.

Material and methods. Organisational model for primary prevention of CVD (the group preventive consulting at the workplace and individualized profound prophylactic consulting in outpatient environment of locomotory depot rehabilitation centre) has been performed for the first group of locomotory teams in 2010–2012 y.; second group was under annual medical observation (screening and medical comission workout). The monitoring of risk factors and analysis of morbidity causing temporary disability (TD) by CVD; direct and indirect expenses calculation; expense-efficacy estimation.

Results. On the background of organisational model for primary CVD prevention in the first group there was a decrease of TD from CVD by 32,8% cases and 34,6% days, from DM by 55,6%; no cases of CHD; total expenses decreased by 44,1%. For three years of observation of 2nd group there was increase of TD from CVD by 19,2% and days — by 8,7%; TD from CHD and DM increased twice; total increase of expenses was by 24,3%. In the 1st group prevalence of smoking decreases 1,6 times and expenses for 1% — decrease of this addiction reached 10304,7 RUR; prevalence of abdominal obesity decreased 1,3 times, expenses for attaining the target waist circumference in 1% patients reached 20310,7 RUR; prevalence of hypercholesterolemia was 1,8 times rarer and expenses to reduce it in 1% patients were 8493,6 RUR by 100 workers. In the 2nd group prevalence of smoking decreased by 4,7% and expenses to reduce this addiction for 1% of men were 107607,4 RUR by 100 workers, that is 10,4 times more than in the 1st group; prevalence of abdominal obesity increased by 5,5%, of hypercholesterolemia — by 4,7%.

Conclusion. Realisation of the organisational model for primary CVD prevention in railway system workers during first 3 years showed clinical and economic efficacy in terms of the main risk factor prevalence decrease, TD decrease and overall expenses for CVD.

Russ J Cardiol 2014, 6 (110): 12–18

Key words: clinical and economic efficacy, primary prevention, railway workers.

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FACTOR ANALYSIS AND INDIVIDUAL PROGNOSIS FOR THE PATIENTS WITH FIRST REVEALED ARTERIAL HYPERTENSION

Salamatina L. V.¹, Zorina L. S.¹, Tokarev S. A.²

Abstract

Aim. To study the risk factor (RF) prevalence, target organ damage (TOD) and overall cardiovascular risk among patients with the first time revealed AH.

Material and methods. Totally 90 patients included (48 women, 42 men) with increased blood pressure (BP) from those who requested medical care for the first time. After investigation the evaluation of cardiovascular risk was done according to National guidelines for Prophylaxy, diagnostics and treatment of AH, scales SCORE and PROCAM.

Results. Most patients had 2 or more RF. Absence of additional cardiovascular risk factors among patients with the first time revealed AH existed only for women; 29,2% women and 14,3% men had 1 RF. The prevalence of 2 RF was the same for both genders: 42,9% and 43,8%, resp. Three and 4 RF were twice more prevalent in men, than in women.

Conclusion. In the population of patients with the first time revealed AH the average and high risk of cardiovascular complications was more common.

Russ J Cardiol 2014, 6 (110): 19–23

Key words: arterial hypertension, cardiovascular risk, prognosis.

¹BI The District Cardiological Dispensary, The Center for Diagnostics and Cardiovascular Surgery, surgut; ²SBIH Yamal-Nenetsky Autonomous District Centre for Medical Prophylaxy, Nadym, Yamal-Nenetsky Autonomous District, Russia.

SELECTION FOR THE QUANTITATIVE EVALUATION METHOD OF CORONARY ARTERIES BASED UPON COMPARATIVE ANALYSIS OF ANGIOGRAPHIC SCALES

Gavrilova N. E., Metelskaya V. A., Perova N. V., Yarovaya E. B., Boytsov S. A., Mazaev V. P.

Abstract

Aim. To conduct a comparative research of a variety of angiographic scales with the aim to choose strict and useful scoring system for coronary artery lesion estimation.

Material and methods. The cohort of patients is investigated with the age of 25–86 y. (n=502, 70,7% males), who at FSBI “SSRCPM” of the Ministry of Health were underwent coronary arteriography. To evaluate the severity of atherosclerosis by the angiography results the scoring systems Gensini and SYNTAX were used. Quantitative evaluation of stenoses was done using the software of “General Electric Innova 4100”.

Results. The groups were formed according to absence, mild or severe coronary atherosclerosis using the Gensini and SYNTAX scores, and also by coronary stenoses prominence. The significant association between all three methods was shown: Spearman correlation coefficient about 0,87. Quantity of points by Gensini and SYNTAX increases according to the quantity of arteries involved. But usage of Gensini score with addition of cut-off points makes more precise the identification of patients with severe coronary arteries lesion.

Conclusion. The Gensini scale and the cut-off points provided makes it possible a relevant estimation of coronary arteries lesion and improves the decision whether to revascularize or not.

Russ J Cardiol 2014, 6 (110): 24–29

Key words: atherosclerosis, coronary arteriography, coronary arteries, angiographic scales.

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INTERRELATION OF METABOLIC SYNDROME COMPONENTS WITH CELL AND VESSEL AGING PARAMETERS

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Abstract

Aim. To study the interrelation of different MS components and parameters of cell and vessel aging.

Material and methods. Totally 136 patients studied with the age 25–75 y. without any signs of CVD or other chronic diseases, not receiving any continuous drug therapy. In all patients the antropometric parameters, BP levels, fasting plasma glucose, HDL cholesterol and triglycerides levels were measured. The PWV measurement was performed by the device SphygmoCor (AtCorMedical, Australia). Telomere length (TL) was measured by PCR.

Results. Multidimensional regression analysis revealed that among all MS risk factors studied only the age (p=0,0003), waist circumference (p=0,0434), systolic BP (p=0,0001), HOMA-IR (p=0,0033), fasting glycemia (p=0,0001) and TL (p=0,0001) are the independent determinants of PWV, and this relation is reversed for TL, but direct — with the other parameters. Independent reversed relation is with TL only for age (p=0,0033) and HOMA-IR (p=0,0027).

Conclusion. Arterial hypertension can be named as the main hemodynamic component and impaired carbohydrate metabolism, insulin resistance and obesity as the main non-hemodynamic components of vessel wall rigidity increase and as the main target for therapeutical intervention.

Russ J Cardiol 2014, 6 (110): 30–34

Key words: arterial stiffness, telomere length, metabolic syndrome, insulin resistance.

FSBI State Scientific-Research Centre for Preventive Medicine of the Ministry of Health, Moscow, Russia.

CARDIOVASCULAR DISEASES OF THE LENINGRAD SIEGE SURVIVORS — NEW RISK FACTORS RESEARCH

Rotar M. P., Moguchaya E. V., Kolesova E. P., Boyarinova M. A., Erina A. M., Dudorova E. A., Ilyina M. A., Solntsev V. N., Konradi A. O.

Abstract

Aim. To assess the influence of starvation on the prevalence of cardiovascular risk factors and diseases in survivors of Leningrad Siege, depending on the starvation occurrence.

Material and methods. Leningrad Siege survivors from Primorsky district of Saint-Petersburg were invited and examined during December 2009 to January 2012. All participants were interviewed by a questionnaire regarding lifestyle, risk factors, cardiovascular disease, comorbidities and medication. Blood pressure (BP) measurements and anthropometry (weight, height, waist and neck circumference) were performed according to standard procedures. Fasting serum lipids and plasma glucose were measured on Hitachi-902. Echocardiography (Vivid 7) and electrocardiography (MAC1200ST) were performed. 305 survivors of Leningrad Siege (224 (73%) females and 81 (27%) males) were examined, the mean age was 70,5 yrs. In the control group were 46 patients with similar gender and age pattern – 31 (67%) females and 15 (33%) males, mean age was 71,3 years. All people were divided in two groups: who was born during the Leningrad Siege (45 (14,7%)) and before the Leningrad Siege (260 (85,3%) subjects) in the period from 1928 to 1941.

Results. Siege survivors had lower anthropometric indexes but higher HDL level comparing with control group. There were no significant differences in the prevalence of cardiovascular disease in 2 groups: only chronic CHD was more often (48,9% vs 33,3%, $p=0,04$) and prevalence of atrial fibrillation was slightly lower (17% vs 8,5%, $p=0,05$) in siege survivors comparing with the controls. Survivors who were undergone the starvation during childhood and adolescent period more often had hypertriglyceridemia comparing with subjects after intrauterine starvation. Diagnosis of myocardial infarction (16 (19,8%) vs 16 (7,2%), $p=0,002$) and AF (13 (16%) vs 12 (5,35%), respectively, $p=0,02$) were detected more often in men comparing with women. Males less often had hypercholesterolemia (39 (48,1%) vs 170 (75,8%), $p<0,0001$) and abdominal obesity (43 (53,0%) vs 162 (72,3%), $p=0,001$) than females.

Conclusions. No significant influence of starvation during Leningrad Siege on cardiovascular risk factors and diseases was revealed. Delayed consequences of starvation appeared to be less important than other risk factors and heredity predisposition.

Russ J Cardiol 2014; 6 (110): 35–41

Key words: Leningrad siege survivors, hypertension, starvation.

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INTERRELATION OF TRANSCUTANEOUS CORONARY INTERVENTIONS FOR ACUTE FORMS OF CORONARY HEART DISEASE AND MORTALITY PARAMETERS IN TYUMEN REGION INHABITANTS

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Abstract

Aim. To find out and evaluate interrelation between inhabitants mortality in Tyumenskaya region and quantity of PCI for ACS in this region during 2006–2012 y.

Material and methods. The data on PCI procedures used that is provided in the information and analytical digests “Cardiovascular surgery. Diseases and inherited anomalies of circulation system”. The data on mortality and morbidity is published in statistical issues of the Health Department of Tyumen region.

Results. During the period studied at the south of Tyumen region there was progressive decrease of morbidity and the quantity of PCI procedures for ACS increased significantly. Negative correlation found for PCI and total mortality ($r=-0,857$, $p=0,014$), total mortality among economically active population ($r=-0,893$, $p=0,007$) cardiovascular mortality ($r=-0,857$, $p=0,014$). The quantity of PCIs for MI was related to general mortality ($r=-0,929$, $p=0,003$), to general mortality of economically active population ($r=-0,964$; $p<0,001$), MI mortality of economically active population ($r=-0,893$; $p=0,007$) and among men of economically active age ($r=-0,893$; $p=0,007$).

Conclusions. The data revealed confirms that the decrease of cardiovascular mortality in Tyumen region is at most relies upon progressing increase of PCI procedures for acute CHD during 2006–2012 y.

Russ J Cardiol 2014, 6 (110): 42–46

Key words: cardiovascular mortality, percutaneous coronary interventions, acute coronary syndrome, myocardial infarction.

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ERECTILE DYSFUNCTION AS EARLY PREDICTOR FOR CARDIOVASCULAR DISEASES IN MEN WITH OBSTRUCTIVE SLEEP APNEA SYNDROME

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Abstract

Aim. To evaluate the pattern of nocturnal penile episodes during polysomnography and the lipid profile for the risk of cardiovascular diseases development in men with OSAS.

Material and methods. Totally 51 men aged 46–55 years participated in the study. After enhanced PSG by the GRASS-TELEFACTOR Twin PSG (Comet) system with As 40 amplifier and integrated module SPM-1 (USA) with in-built into the software option for nocturnal penile episodes (NPT) registration the participants were divided into 2 groups. First 37 men made up the group of OSAS patients (av. age 53,16±3,45 y., body mass index — 33,19±5,76 kg/m²). Other 14 men were the control, with the same age and BMI, but free from respiration disorders during the night sleep. The serum utilized as the specimen for chemistry.

Results. In men with OSAS the disorder sleep structure was found, represented by significant prevalence of low-deepness sleep, deep sleep deficiency and lack of REM sleep. Also there was impairment of night spontaneous erection during REM sleep – retardation of the

beginning and prolongation of detumescence. The quantity of NPT was lower during the sleep. Lipid profile showed lower levels of antiatherogenic and increased levels of atherogenic cholesterol fractions with increased atherogenicity index. Relative risk for cardiovascular pathology was 4 times higher in patients erectile dysfunction (RR=3,9; 95% CI 1,44–10,61). Attributive risk for ED in regard to cardiovascular pathology was 66% (95% CI 44,6%–87,4%).

Conclusion. The results make possible to regard the ED in OSAS as early predictor for cardiovascular pathology in men.

Russ J Cardiol 2014, 6 (110): 47–51

Key words: erectile dysfunction, obstructive sleep apnea syndrome, lipid profile, atherosclerosis.

FSBI The Scientific Centre for the Family Health and Reproduction Problems of Siberian Dept RAMS, Irkutsk, Russia.

THE INFLUENCE OF OBSTRUCTIVE SLEEP APNEA SYNDROME ON LIPID METABOLISM AND ATHEROSCLEROTIC LESION OF CAROTID ARTERIES IN PATIENTS WITH ARTERIAL HYPERTENSION

Statsenko M. E., Talagaev S. V.

Abstract

Aim. To study an interrelation between obstructive sleep apnea syndrome with lipid metabolism disorders and atherosclerotic lesion of carotid arteries in patients with arterial hypertension.

Material and methods. The article presents the results on the study of 150 patients with arterial hypertension, of those 75 also had obstructive sleep apnea syndrome (main group); 75 patients without apnea constituted control group. This study included patients with variable body mass index — from normal values (18,5–24,9 kg/m²) to 2–3 grade obesity.

Results. A reliable correlation interrelation was found for the sleep apnea episodes quantity during the night and risk of different types of hyperlipidemias, with intima\media thickness in carotid arteries.

Conclusion. It is ascertained that in the main group prevalence of dyslipidemias of IIa and IIb types is higher as atherosclerotic lesion.

Russ J Cardiol 2014, 6 (110): 52–56

Key words: arterial hypertension, obstructive sleep apnea syndrome, body mass index, hyperlipidemia, atherosclerosis of carotid arteries.

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ASSOCIATION OF ELECTROCARDIOGRAPHIC MARKERS OF METABOLIC CARDIOMYOPATHY WITH LONG-TERM RESULTS OF MYOCARDIAL REVASCULARIZATION IN MEN WITH CORONARY ATHEROSCLEROSIS

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Abstract

Aim. To study electrocardiographic (ECG) markers of metabolic cardiomyopathy (MC) in men with coronary atherosclerosis (CA) in association with 5-year long-term results of coronary artery bypass grafting (CABG).

Material and methods. The study included 77 men aged 42–77 years with stenotic CA verified during selective coronary angiography (CAG) without acute coronary syndrome (ACS) and stable angina FC II–IV — the inhabitants of Western Siberia, admitted to the hospital for CABG. All patients before CABG underwent ECG at rest in 12 standard leads, followed by coding Minnesota code. We analyzed ECG markers of MC, as the length of the interval QT, corrected interval QT, ST segment above the contour >5mm, ST segment depression below the contour >5mm non-ischemic type, T-wave changes (flattening or reduction of amplitude), the inversions, syndrome TV1>TV6 (amplitude of T in V1 exceeds the amplitude of T in V6), signs of left ventricular hypertrophy (LVH), arrhythmias and conduction disorder.

Results. In men with CA before the CABG registered the following ECG markers MK: arrhythmias in 38 patients, LVH — in 55, the syndrome TV1>TV6 — in 24, the change of the T wave — in 58, segment ST elevation — in 44, segment ST depression — in 23, prolongation of the interval QT — in 5. The results were obtained in 5-year course of CA after surgical myocardial revascularization. The group of men with complicated CA (adverse long-term prognosis) was revealed. A positive correlation between the presence of the syndrome TV1>TV6 and fatal outcomes in the long term was found. The relative risk of death during 5-year period after CABG in patients with the syndrome TV1>TV6 was higher than in the group without the syndrome. In patients with the TV1>TV6 syndrome the relative risk of unfavourable later period as a whole (death, myocardial infarction, reoperation) was higher than of favourable. A positive correlations between ST-segment elevation before CABG and long term fatal outcomes, and in general, an unfavourable long term prognosis, were found. In patients with ST-segment elevation the relative risk of unfavourable later period is generally higher than of favourable.

Conclusion. There is an association of electrocardiographic markers of MK (syndrome TV1>TV6, segment ST elevation) with 5-year long-term results of coronary revascularization in men with coronary atherosclerosis.

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Key words: electrocardiographic markers, metabolic cardiomyopathy, coronary atherosclerosis, myocardial revascularization.

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BLOOD PRESSURE VARIABILITY AND THE CONDITION OF TARGET ORGANS IN MENOPAUSAL WOMEN

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Abstract

Aim. To study the correlation of arterial pressure variability on brachial artery and central arterial pressure variability with condition of target organs among menopausal women.

Material and methods. This research included 93 women of menopause age — 37 premenopausal women and 56 women at early postmenopause. The age was 49,1 (48,0; 51,0) and 53,9 (50,0; 56,0), resp. Of those 69 (74,2%) had arterial hypertension. No one received continuous antihypertension therapy. 24-hour blood pressure monitoring with variability estimating of systolic and diastolic pressure and evaluation of arterial stiffness was taken by oscillometric method. Daily index of arterial stiffness, ambulatory index of arterial stiffness, augmentation index and indicators of central aortal pressure were estimated. Echocardiogram was used for left ventricular remodeling estimation. Pulse wave velocity was measured by ultrasonic method. Vascular regulation of endothelium of brachial artery was estimated by the test of reactive hyperemia. As a sign of large elastic arteries remodeling the intima-media thickness was used. All women with arterial hypertension divided into 2 groups depending on variability of arterial pressure — 16 women with high levels of systolic and diastolic arterial pressure were in first group and 53 women with normal indicators of variability were in second group. Control group consisted of 24 women that had no arterial hypertension with normal indicators of arterial pressure variability.

Results. Disordered arterial pressure was prevalent among women in early postmenopause. Raise of variability of arterial pressure was correlated with morphofunctional changes of the heart, structure-functional vascular changes, increase of arterial stiffness, disturbances of endothelial vascular regulation and subclinical kidneys damage.

Conclusion. Central arterial pressure variability has no additional advantages in comparison with estimated variability of brachial artery pressure. Increased variability of arterial pressure among menopausal women can be considered as additional factor of target organ damage in early stages of climacteric.

Russ J Cardiol 2014, 6 (110): 62–70

Key words: menopause, arterial hypertension, variability of arterial pressure, damage of target organs, arterial stiffness, central aortic pressure.

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ANTIPLATELET THERAPY IN PROPHYLAXY OF NEGATIVE CARDIOVASCULAR EVENTS AFTER CORONARY REVASCULARIZATION. IS THERE A CONSENSUS?

Grinshtein Yu. I., Kosinova A. A., Grinshtein I. Yu.

Abstract

The review provides the current information about the role of antiplatelet therapy in the cardiovascular prevention in patients with coronary artery disease and coronary revascularization. Recent drugs as components of dual antiplatelet therapy after percutaneous interventions are considered. The review includes features of antiplatelet therapy after coronary bypass surgery. The paper contains points of European and American recommendations. Authors discuss the controversial and unsolved issues of antiplatelet therapy. The necessity for new dosing forms synthesis and further research for development effective prevention of adverse cardiovascular events after coronary revascularization is noted.

Russ J Cardiol 2014, 6 (110): 71–76

Key words: cardiovascular prevention, antiplatelet drugs, percutaneous coronary intervention, coronary artery bypass grafting.

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GENDER AND AGE DIFFERENCES OF BRAIN NATRIURETIC PEPTIDE CONCENTRATION IN PATIENTS WITH MYOCARDIAL INFARCTION

Usoltseva E. N., Tavluva E. V., Barbarash O. L.

Abstract

Aim. To measure the changes in brain natriuretic peptide (NT-proBNP) in patients with acute myocardial infarction with ST segment elevation (STEMI) according to the age and gender.

Material and methods. Totally 223 patients with STEMI included, of those 167 (74,88%) were men and 56 (25,11%) women. Average age of women was 61,80 (57;68) years, of men — 57,15 (51;63) years ($p=0,0003$). The follow-up period starting during hospitalization included 12 months of outpatient treatment. After 12 months the endpoints were assessed. The NT-proBNP concentration was measured on 10–14th day after infarction using serum by testing system “BIOMEDICA GRUPPE”.

Results. In women from older group NT-proBNP concentration was higher than in younger patients by 38%, in men — by 57,31%. In men with poor prognosis level of NT-proBNP was significantly higher (96,35 fM/ml) comparing to those with benign prognosis (63,8), $p=0,0108$. There were no such differences in women.

Conclusion. Trustworthy differences of the biomarker studied between men and women do not exist, however in men and in women either of older group (more than 65) there are higher levels of NT-proBNP, than in younger group. Also men with poor prognosis in higher age group do have the highest NT-proBNP level.

Russ J Cardiol 2014, 7 (111): 81–86

Key words: gender differences, age, brain natriuretic peptide.

FSBI SII of Complex Cardiovascular Diseases of the Siberian Dept of RAMS, Kemerovo, Russia.

THE VALUES OF MATRIX METALLOPROTEASE-9 AND TISSUE METALLOPROTEASE INHIBITOR-1 IN ACUTE MYOCARDIAL INFARCTION WITH ANEURYSM FORMATION

Govorin A. V.¹, Ratsina E. V.^{1,2}, Sokolova N. A.¹, Fetisova N. V.¹

Abstract

Aim. To study the blood levels of MMP-9 and TIMP-1 in dynamic in patients with acute transmural anterior myocardial infarction complicated by aneurysm.

Material and methods. 46 patients with acute transmural anterior myocardial infarction were included into the study. The blood levels of MMP-9 and TIMP-1 were studied.

Results. In 1–3 days the patients with myocardial infarction without aneurysm had a significant increase in MMP-9 up to 229,8 ng/ml, then to 10–12th days a decrease and then increase again up to 237,3 ng/ml by 18–22th days. In patients with myocardial infarction complicated by an aneurysm at 1–3rd and 10–12th days the level of MMP-9 increased slightly, and only at 18–22th days we observed significant increases of MMP-9 up to 159,2 ng/ml. In patients with myocardial infarction without aneurysm the level of TIMP-1 gradually grew up from 1–3rd days (698,9 ng/ml) to 18–22th days (942,3 ng/ml). In patients with myocardial infarction complicated by an aneurysm at 1–3rd and 10–12th days we observed maximum values of TIMP-1, gradually decreased to 18–22th days.

Conclusion. The changes found in MMP-9 and TIMP-1 levels might indicate a delay of reparation processes in patients with myocardial infarction complicated by an aneurysm.

Russ J Cardiol 2014, 7 (111): 87–90

Key words: acute transmural anterior myocardial infarction, aneurysm, extracellular matrix, MMP-9, TIMP-1.

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THE OUTCOMES OF STEMI IN PATIENTS WITH COPD IN KEMEROVO REGION

Polikutina O. M., Slepynina Yu. S., Bazdyrev E. D., Karetnikova V. N., Barbarash O. L.

Abstract

Aim. To study the immediate and long-term outcomes of STEMI in patients with concomitant COPD in Kuzbass.

Material and methods. Totally 529 patients with STEMI included. They were divided into 2 groups: 1st — patients with COPD diagnosed before (65 pts., 12,3%), 2nd — patients without COPD (464 pts. — 87,7%). The diagnosis of COPD was verified by anamnesis morbi in outpatient records. At admittance all patients underwent coronary angiography and angioplastic with infarct-depending artery stenting. Laboratory values were assessed by 10–14 days after MI.

Results. There was higher prevalence of complicated in-hospital MI course in patients with STEMI and COPD. In-hospital mortality was also higher. After 1 year more endpoints registered for those with COPD. In this group the levels of NT-proBNP at the 10th after MI were higher.

Conclusion. In Kemerovo region the prevalence of COPD in patients with STEMI was 12,3%. COPD was associated with poor outcomes in hospital and long-term periods and with more complications. This should be taken into account during patient assessment to create groups of higher risk in the industry-rich region to improve healthcare.

Russ J Cardiol 2014, 7 (111): 91–97

Key words: ST elevation myocardial infarction, chronic obstructive pulmonary disease, comorbidity.

FSBI SII of Complex Cardiovascular Diseases of the Siberian Dept of RAMS, Kemerovo, Russia.

THE MARKERS OF OXIDATIVE STRESS IN PATIENTS WITH ACUTE MYOCARDIAL INFARCTION WITH NON-ALCOHOLIC FATTY LIVER DISEASE

Belaya I. E.

Abstract

Aim. To study plasma lipid profile, systemic inflammation and endothelial function in patients with acute period of MI with Q-wave and liver steatosis (LS) or non-alcoholic steatohepatitis (NASH).

Material and methods. Totally 48 patients with acute MI of the left ventricle were studied (1st group), with average age 66,33±1,66; 53 — with acute MI and LS (2nd group) — average age 63,74±1,87, and 7 — with acute MI and NASH (3rd group) — average age

58,86±4,47. In all groups men dominated. We measured the levels of liver enzymes, bilirubin, total cholesterol, LDP cholesterol, VLDL cholesterol, triglycerides, atherogenicity coefficient, cholesterol-accepting properties of HDL, level of nitrite- and nitrate-anions in serum, hsC-reactive protein.

Results. The disordered lipid profile in patients of both groups shows the increased levels of total cholesterol, LDL ($p<0,001$) and VLDL ($p<0,01$), atherogenicity coefficient ($p<0,001$) and lowering of HDL and their cholesterol-accepting properties ($p<0,001$). In patients of 2nd and 3rd groups there is an increase of nitrites ($p<0,001$) and nitrates ($p<0,001$). Endothelial dysfunction was the worse in acute MI with NASH. In patients with combined pathology there is increase of C-reactive protein ($p<0,001$). The parameter of systemic inflammation is higher in patients with acute MI with NASH.

Conclusion. In patients with combined MI and LS or NASH there is an increase of atherogenicity and decrease of anti-atherogenicity in lipid profile, increase of stable NO metabolites with maximally prominent endothelial dysfunction in patients with NASH, due to aseptic inflammation. Marker of inflammation severity is higher in those with NASH comparing to LS.

Russ J Cardiol 2014, 7 (111): 98–104

Key words: lipid plasma profile, nitric oxide, C-reactive protein, myocardial infarction, liver steatosis, non-alcoholic hepatitis.

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CLINIC AND PHARMACOTHERAPY

AN ADAPTOGEN USAGE IN OUTPATIENT PRACTICE TO IMPROVE CARDIOVASCULAR ADAPTATION TO ABNORMAL CLIMATIC CONDITIONS (THE HEAT)

Smirnova M. D., Svirida O. N., Ageev F. T., Fofanova T. V., Vitsenya M. V., Mikhailov G. V., Kononova G. G., Tikhaze A. K., Lankin V. Z.

Abstract

Aim. To evaluate the drug implied to improve the metabolic resistance to stress (adaptogen), QudesanR, on its influence on cardiovascular system, psychological status and life quality of patients with average to high cardiovascular risk in the extreme climatic conditions (the summer heat).

Material and methods. We included 60 patients; for 30 of those the QudesanR 40 gtts. qd was added to standard drug therapy; other 30 patients were controls. We measured office BP, potassium and sodium concentrations; malonic dialdehyde (MDA), superoxidedismutase (SOD) in erythrocytes. Then the relation of MDA/SOD was calculate. Patients also completed the questionnaire made up for this study.

Results. In the QudesanR group during the heat period we found lowering of SBP ($\Delta -13,8$ mmHg, $p=0,02$), DBP ($\Delta -4,5$ mmHg, $p=0,05$) and PWV ($\Delta -0,8$ m/s, $p=0,05$) absent in the control. Also in QudesanR group the concentration of sodium starts to increase during the heat period ($\Delta +1,0$ mM/l, $p=0,008$). This increase becomes significant by september ($\Delta +1,7$ mM/l, $p=0,008$) and is probably adaptive. The level of MDA ($p<0,05$) and MDA/SOD relation, the signs of "antioxydant potential", in blood were increasing significantly during the summer heat only in control group. The complaints on heart rhythm disorders ($p=0,04$) and on CHF worsening ($p=0,09$) after the end of heat period were more common in control group. That is the QudesanR shows adaptogenic effect and can be used to improve adaptability during the heat period and its switching to colder time in patients with compensated CVD.

Russ J Cardiol 2014, 5 (109): 101–108

Key words: the heat wave, QudesanR, heat adaptation, cardiovascular risk.

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MODERN APPROACHES TO THE TREATMENT OF HYPERCHOLESTEROLEMIA IN CORONARY HEART DISEASE PATIENTS WITH METABOLIC SYNDROME AND CHRONIC NON-ALCOHOLIC STEATOHEPATITIS

Osadchuk M. A., Butorova L. I., Solodenkova K. S., Tokmulina G. M.

Abstract

Aim. To assess safety and effectiveness of combination therapy by simvastatin with ursodeoxycholic acid in treatment of dyslipidemia in coronary heart disease patients.

Material and methods. Totally 30 CHD patients (stable angina, 2nd functional class — 2FC) having metabolic syndrome (MS) had combination therapy by simvastatin (20 mg/day) and ursodeoxycholic acid (Ursosan in daily dose 15 mg per kg) during 30 days. For all included patients the non-alcoholic steatohepatitis (NASH) was confirmed. Of them 25 (85%) had clinical predictors of fibrosis and liver cirrhosis. All patients had abnormal bodyweight and arterial hypertension, very high risk of cardiovascular complications (CCC).

Results. After 30 days of therapy there was significant lowering of ALT from 83,61 (1,81, 5,49) to 51,32 (2,41, 5,76) ME/l, a AST — from 78,44 (2,02, 4,23) to 42,12 (1,99, 6,32) ME/l (mediana). In 7 patients levels of ALT and AST were normal. Also there was significant lowering of dyslipidemia: in 19 (63,3%) there was normalization of some lipid profile components, and in 9 (30%) we reached target LDL cholesterol 1,8 mmol/l. Also there was tendency to bodyweight normalization: BMI decreased by 1,28 kg/m² in men and by 2,35 kg/m² in women. During the study we did not find any significant side effects. All patients completed the course of simvastatin plus UDCA.

Conclusion. Combination treatment by simvastatin and UDCA makes possible the achievement of lipid profile parameters significant improvement and the decrease of serum transaminase activity in patients with CHD and NASH. If not contraindicated, statins and UDCA can be recommended in CHD and non-alcoholic liver disease to reduce the risk of CCC.

Russ J Cardiol 2014, 7 (111): 105–109

Key words: ischemic heart disease, dyslipidemia, obesity, fatty liver disease, statins, ursodeoxycholic acid.

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CLINICAL CASE

A CASE OF PAINLESS MYOCARDIAL INFARCTION DUE TO BRIDGING OF LEFT ANTERIOR DESCENDING ARTERY

Bogomolova O. S., Furman N. V., Titkov I. V.

Abstract

Myocardial bridging (MB) is congenital abnormality of the coronary arteries, which typically does not interfere with long term prognosis, but in some cases can cause myocardial infarction and other life-threatening conditions. This article reviews current knowledge about the anatomy, pathophysiology, clinical relevance, and treatment of MB and demonstrates a case of painless myocardial infarction in patients with MB of the left anterior descending artery.

Russ J Cardiol 2014, 7 (111): 110–112

Key words: myocardial bridging, myocardial infarction.

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LITERATURE REVIEWS

DIHYDROPYRIDINE CALCIUM ANTAGONISTS AND THE TREATMENT OF ARTERIAL HYPERTENSION AND OBESITY PATIENTS IN ACCORDANCE WITH THE MODERN CLINICAL GUIDELINES

Gilyarevskiy S. R.¹, Goldschmidt M. V.¹, Kuzmina I. M.²

Abstract

This review discusses the potential of a combination antihypertensive therapy with lercanidipine, a dihydropyridine calcium antagonist, for the achievement of target blood pressure levels.

Russ J Cardiol 2014, 4 (108): 113–119

Key words: blood pressure, lercanidipine.

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THE RELEVANCE OF THROMBOLYTIC THERAPY IN ST ELEVATION MYOCARDIAL INFARCTION

Teplova N. V., Taratukhin E. O.

Abstract

The article is about contemporary views on thrombolytic drugs usage. Although there is a great improvement in endovascular treatments, systemic thrombolysis is still one of the most important approaches to MI with ST elevation. The data of a few studies of thrombolytics with percutaneous intervention is provided, as with it or instead of it. Also the importance of thrombolytic drug pharmacokinetic profile is underlined.

Russ J Cardiol 2014, 5 (109): 109–112

Key words: myocardial infarction, ST segment elevation, thrombolysis, percutaneous intervention, tenecteplase.

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TELOMERES AND ARTERIAL HYPERTENSION: PATHOPHYSIOLOGY AND CLINICAL PERSPECTIVES

Kobalava J. D., Kotovskaya Yu. V.

Abstract

The ageing is the main risk factor for arterial hypertension (AH) and cardiovascular diseases. Natural ageing with normal BP is followed by changes in large arteries (rigidity), myocardium (hypertrophy) and diastolic relaxation and filling of cardiac muscle (diastolic dysfunction). In AH these changes develop earlier and progress faster. These can be found at any age in AH. The telomere length (TL) — a special terminal structures on somatic cells chromosomes — is dependent on the age and is being shortened with age. This review concerns modern views on the role of telomeres as biological markers of ageing to understand the pathophysiology of essential arterial hypertension as a syndrome of accelerated cardiovascular system ageing.

Russ J Cardiol 2014, 6 (110): 77–84

Key words: arterial hypertension, telomeres, accelerated cardiovascular ageing.

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THE DECREASE OF SODIUM CHLORIDE CONSUMPTION. EFFICACY OF PREVENTIVE STRATEGY. PART V

Poteshkina N. G.

Abstract

The article concerns the review of different approaches to reduce table salt consumption by human beings. The levels for harmless consumption are reviewed those were recommended in terms of target organ damage prevention. The guidelines for salt consumption consuming regulation are presented, that are in use in various world countries. The foundations for personal, social and state policy for practical implication of these guidelines are provided. The predicted outcomes for the realization of the policy in relation to decrease of general and cardiovascular mortality and also correction of arterial hypertension are given. The article can be in the field of interest of physicians — internists of broader profile, cardiologists, health managers.

Russ J Cardiol 2014, 6 (110): 85–92

Key words: salt consumption, general and cardiovascular morbidity and mortality, arterial hypertension, social and state policy.

SBEI HPE Russian National Research Medical University n. a. Pirogov of the Ministry of Health, Moscow, Russia.

LECTURE

PHYSICAL TRAINING IN THE REHABILITATION AND PREVENTION IN PATIENTS WITH ISCHEMIC HEART DISEASE AFTER PERCUTANEOUS CORONARY INTERVENTIONS: THE BORDERS OF EFFICIENCY AND SAFETY

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Abstract

Currently, it is proved that physical training (FT) should be a compulsory component of programmes for complex rehabilitation of patients with coronary heart disease after PCI. However, given the heterogeneity of clinical status of patients after conducting PCI medical rehabilitation should be personalized as for the choice of intensity and exposure of FT and with obligatory monitoring of their effectiveness and safety. This greatly extends the possibilities of wide use of FT at the stage of rehabilitation in the real clinical practice.

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Key words: physical training of various intensity, percutaneous coronary intervention, rehabilitation.

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JUBILEE

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AD MEMORIAM

THE FATHER AND THE SON KASSIRSKY – PRIDE OF NATIVE CARDIOLOGY (FOR THE 85TH ANNIVERSARY OF THE HONORARY SCIENTIST PROFESSOR G. I. KASSIRSKY)

Bokeriya L. A., Glantsev S. P., Nevedrova M. N.

Abstract

The article is dedicated to the memory of professor G. I. Kassirsky, one of the founders of the novel direction in fatherhood cardiology — cardiorehabilitation. The biography, data on scientific works and adherents provided.

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