· Advances in Medical Sciences · Vol. 58(2) · 2013 · pp 320-325 · DOI: 10.2478/ams-2013-0003

The role of Interleukin-6, its –174 G>C polymorphism and C-reactive protein in idiopathic cardiac arrhythmias in children

Szydlowski L[1,*], Skierska A[1], Markiewicz-Loskot G[2], Mazurek B[1], Morka A[1], Undas A[3]

1 Department of Pediatric Cardiology, Medical University of Silesia in Katowice, Katowice, Poland
2 Department of Nursing and Social Medical Problems, Medical University of Silesia in Katowice, Katowice, Poland
3 Institute of Cardiology, Jagiellonian University School of Medicine, Cracow, Poland

* CORRESPONDING AUTHOR:
Department of Pediatric Cardiology,
Medical University of Silesia in Katowice,
Medykow 16,
40-752 Katowice, Poland
Tel.: + 4832 207 1855
Fax: + 4832 207 1854
e-mail: szydlowskil@interia.pl (Leslaw Szydlowski)

Received: 14.01.2013
Accepted: 07.03.2013
Advances in Medical Sciences
Vol. 58(2) 2013 · pp 320-325
DOI: 10.2478/ams-2013-0003

ABSTRACT

Purpose: Knowledge about the role of inflammation in the pathogenesis of arrhythmias in children is limited. Several studies have suggested a relationship between plasma IL-6 levels and/or the -174G>C IL-6 gene polymorphism and atrial fibrillation in adults. Our present study was performed to investigate whether serum IL-6, -174G>C IL-6 polymorphism and C-reactive protein (CRP) are associated with arrhythmias of unknown origin in children.

Methods: The study included 126 children diagnosed with supraventricular or ventricular arrhythmia. Patients with congenital heart defects as well as arrhythmias of known origin were excluded from the study. The control group comprised 37 healthy children. The 24 hour Holter electrocardiography monitoring was performed. Serum IL-6, –174 GC IL-6 polymorphism and CRP concentrations were measured on admission.

Results: There were no differences in IL-6, CRP and –174 G>C IL-6 genotype distribution between the control and patient groups. No significant differences in IL-6, CRP and –174 G>C IL-6 genotypes were observed between children with supraventricular or ventricular arrhythmias. The severity of arrhythmias showed also no associations with IL-6, CRP or –174 G>C IL-6 genotypes.

Conclusion: The results suggest that idiopathic cardiac arrhythmias of unknown origin in children are not associated with selected pro-inflammatory markers of infections i.e. elevated IL-6, CRP or –174 G>C IL-6 polymorphism. This new information can effectively reduce the total financial cost of unnecessary diagnosis and treatment of children affected by cardiac arrhythmias.

Key words: : Arrhythmia, children, gene polymorphism, C-reactive protein, interleukin-6.

INTRODUCTION

Interleukin-6 (IL-6) and C-reactive protein (CRP), largely regulated by IL-6 production, are both implicated in the pathogenesis of cardiovascular disorders. The IL-6 –174 G>C promoter polymorphism has been shown to be associated with serum IL-6 and/or CRP levels, however, data on these links are inconsistent [1-3]. Moreover, there is growing evidence suggesting the involvement of the IL-6 –174 G>C promoter polymorphism in various cardiovascular disorders, including acute coronary syndrome, arterial hypertension and atherosclerotic vascular disease [4-6]. It has been demonstrated, that IL-6 -174 GG genotype is an independent predictor of cardiovascular death after an acute coronary syndrome [7-8], while other studies failed to confirm this association [9]. Recently, a number of studies have demonstrated an increased prevalence of atrial fibrillation (AF) in adult subjects with elevated levels of IL-6

and/or CRP [10-14]. Data on the associations between these inflammatory markers and other types of arrhythmia are sparse. Inflammatory state is associated with a future risk of AF, which has led to the hypothesis that atrial arrhythmias may result in intracardiac sequestration of inflammatory cytokines in the heart [15]. The study by Li et al. [16] showed that patients with AF had elevated levels of hs-CRP and IL-6. Increased plasma IL-6 and CRP levels may be an independent predictor of stroke in AF patients. In contrast to adults, AF occurs incidentally in children, and a potential role of inflammatory factors and their genetic determinants in arrhythmias in children has not been studied in a larger group of patients. There have been reports showing links between cardiac arrhythmias in children, mainly neonates, and viral infections, including acute Coxsackie B2 myocarditis [17], influenza B virus infection [18], varicella [19], as well as enterovirus and influenza A myocarditis [20], usually complicated by cardiac dysfunction. Arrhythmia, due to viral infection, may be responsible in some cases for sudden infant death syndrome (SIDS), when viral and bacterial toxins induce cytokine activity [21]. In consequence, uncontrolled inflammatory mediators could be involved in some individuals with this disorder. In infants, arrhythmias may be also secondary to respiratory syncytial virus (RSV) infections, particularly when pericarditis or myocarditis is observed [22]. Generally, each infection of the heart might be associated with cardiac complications secondary to viremia and generate cardiac arrhythmias [23-25]. It is unknown which factor may trigger cardiac arrhythmias in older children after excluding obvious cardiac defects and other detectable pathologies. Kowalewski et al. [26] evaluated IL-6, tumour necrosis factor-alpha and cardiac troponin I (cTnI) in young patients with ventricular arrhythmias and noted elevated levels of proinflammatory cytokines, suggesting inflammatory background of ventricular arrhythmias in young people.

We hypothesized, that elevated IL-6 and its –174G>C promoter polymorphism are involved in cardiac arrhythmias in individuals aged 16 years or less. The aim of the present study was to assess potential relationships between IL-6, CRP and IL-6 –174 G>C polymorphism in a large group of consecutive arrhythmic children not presenting with any signs or symptoms of acute infection.

MATERIALS AND METHODS

We enrolled 126 consecutive patients (66 M, 60 F) aged <18 years referred to the Department of Paediatric Cardiology between January 2008 and December 2009, due to first-ever cardiac arrhythmias. The exclusion criteria included congenital heart defects (for example Ebstein's anomaly, right atrial isomerism, abnormalities in atrioventricular connections), surgery or invasive intervention preceding the onset of arrhythmia, known genetic or familial background of arrhythmias, as well as, systemic disease (muscular dystrophy, juvenile rheumatoid arthritis, glycogen storage diseases, thyroid abnormalities). Children were excluded from the study if they had acute infection, diabetes, elevated blood pressure, electrolyte imbalance or were taking any medications on a regular basis. The control group comprised of 37 (21 M, 16 F) healthy children matched for age, sex and body mass index (BMI), recruited at the same time in the same centre.

The Ethical Committee of the Medical University of Silesia in Katowice approved the study (Ref No. KNW-06501-25/I/08), and written, informed consent was obtained from parent and each patient aged 14 years or more.

The diagnosis of arrhythmia was established using the Reynolds Holter 24 hours monitoring system. Based on the type of arrhythmia the study group was divided into two subgroups.

The first subgroup consisted of patients with ventricular arrhythmias (single ventricular extrasystoles, incidents of couplets, triplets, ventricular tachycardia, ventricular flutter or fibrillation) while the second group included supraventricular arrhythmias (supraventricular extrasystoles, supraventricular tachycardia and atrial flutter or AF). The study group was also divided based on the number of cardiac arrhythmias found in 24 hours Holter monitoring: less than 1000/24 hours, 1-10,000/24 hours, and more than 10,000/24 hours. We also created a separate subgroup for atrial or ventricular tachycardia.

We performed transthoracic echocardiography using a Philips 7500 machine with 3-7MHz transducers to exclude congenital heart defects.

High-sensitivity CRP was measured by an immunoturbidimetric assay (Dade Behring Marburg GmbH, Marburg, Germany). A commercially available immunoenzymatic assay (R&D Systems, Minneapolis, USA) was used to determine serum IL-6 levels. The minimal detectable IL-6 concentration was 0.03 pg/ml. All the measurements were performed by technicians blinded to the origin of the samples. Intra-assay and inter-assay coefficients of variation for all laboratory variables were <7%.

DNA extraction and genotyping

DNA was extracted from whole blood or a buffy coat according to the manufacturer's protocol using the GenElute™ Blood Genomic DNA Kit (Sigma-Aldrich) and stored at -20°C until analysis. Polymorphism in the promoter of the IL-6 encoding gene IL-6, -174G>C (rs1800795) was determined by using TaqMan SNP genotyping technique on an ABI PRISM® 7900HT Fast Real–Time PCR System (Applied Biosystems).

Statistical analysis

The data were expressed as the mean ± SD or median (interquartile range). The Shapiro-Wilk test was used to

assess conformity with a normal distribution. Qualitative data were compared by the Pearson's chi-square test or two-tailed Fisher's exact test, as appropriate. Variables with non-normal distributions were analysed by the Mann-Whitney U-test and presented as the median (IQR). Likewise, for correlations, a Spearman's rank correlation coefficient was calculated. A p-value <0.05 was considered statistically significant.

RESULTS

The final analysis included 126 children diagnosed with supraventricular (SV subgroup, n=63) or ventricular (V subgroup, n=63) arrhythmias. Transthoracic echocardiography showed normal cardiac anatomy and function in all the study participants.

Characteristics of the patient and control groups are summarized in *Tab. 1*. No differences were observed between both subgroups (SV versus V) with regard to age (P=0.08), sex (P=0.86) or BMI (P=0.39) and no patients demonstrated symptoms of acute infection confirmed in the clinical as well as laboratory investigations.

Also, serum IL-6 and CRP levels did not differ between the two subgroups (P=0.25, P=0.52), as well as, there were no correlations between either IL-6 or CRP and age, sex, BMI or time from the onset of arrhythmia in the SV versus V subgroups (data not shown).

Genotypes of the –174 G>C IL-6 polymorphism were obtained in all the study participants, except for a single control subject. Genotype distributions of –174 G>C IL-6 polymorphism were in Hardy-Weinberg equilibrium in all the study subgroups (supraventricular arrhythmia, P=0.99; ventricular arrhythmia, P=0.91; controls, P=0.79). No significant pairwise differences in the distribution of the –174 G>C Il-6 polymorphism were observed between the study subgroups in any genetic model (*Tab. 1*). Furthermore, the IL-6 –174G>C polymorphism was not significantly associated with IL-6 or CRP levels in any of the study subgroups (data not shown).

The consecutive analysis focused on the categories of intensity of arrhythmias (*Tab. 2*). The most frequent extrasystoles were 1000-10 000/24 hours (noted in 37 patients), while the least common–fewer than 1000/24h (appeared in 22 cases). The intensity of arrhythmia showed no associations with age (P=0.27), sex (P=0.66) or BMI (P=0.70) in any study group. Concentrations of IL-6 did not differ between groups of various degree of the intensity of arrhythmias (P=0.73). Genotypes of the –174 G>C IL-6 polymorphism were similarly distributed in all the arrhythmia intensity categories (P=0.99). This also held true for CRP levels (P=0.34).

DISCUSSION

To the best of our knowledge, the current study is the largest analysis of school-age children with cardiac arrhythmias of unknown origin in the context of IL-6-mediated inflammatory pathways and genetic determinants. We have here demonstrated that children with supraventricular or ventricular arrhythmias, aged 8-16 years, free of any chronic known cardiac disorders or systemic diseases, did not have increased IL-6 or CRP as compared with well-matched controls. Moreover, our findings clearly indicate that the -174G>C IL-6 polymorphism does not represent the genetic background of cardiac arrhythmias in such a patient population and does not appear to affect circulating IL-6 concentrations. Our findings also show that systemic inflammatory state driven by IL-6 does not contribute to the occurrence of cardiac arrhythmias in children aged 8-16 years. Given the fact that these inflammatory markers showed correlations with the risk of AF [12-16], it seems likely that in children with other arrhythmias, usually transient, short-lived, first-ever episodes, the impact of IL-6-mediated inflammatory response and its genetic modulator is negligible. However, we cannot exclude that the role of this cytokine is more pronounced in children with chronic or acute diseases known to enhance IL-6 synthesis, for example autoimmune diseases.

In children, cardiac arrhythmias are infrequent and most of the cases are recognized to be triggered by unknown causes. A low prevalence of cardiac arrhythmias in children contributes to the fact that our understanding of their etiology and pathogenesis is limited. The condition may occur in all age groups, including the fetus and neonates [17,19].

Beaufort-Krol et al. [27] studied the natural history of premature ventricular beats in children without cardiac structural abnormalities but affected by right or left bundle branch block. The authors found differences between arrhythmias originating from the right or left ventricle. This interesting report suggests that some arrhythmias may disappear spontaneously during childhood, especially those that originate from the right ventricle in contrast to the left.

To our knowledge, the involvement of the two inflammatory factors, namely IL-6 and CRP, in the pathogenesis of cardiac arrhythmias has been systematically investigated in children. For this reason, the current, though negative, study increases our knowledge on the pathophysiology of cardiac arrhythmias in children, suggesting that non-inflammatory mechanisms, yet to be determined, are likely to play a major role.

Ectopic atrial arrhythmias in children may result in left ventricular dysfunction. Wang et al. [28] pointed out that arrhythmias in children might vary from those in adults because of immature myocardium, as well as different electrophysiological characteristics of the conduction system in the pediatric population. In the study group, involving 24 children with arrhythmia, we observed 4 cases with

Table 2. **Effect of various arrhythmias on the variables tested.**

	Categories of Intensity (per 24 hours)				P-values						
	<1,000 (n = 22)	1,000-10,000 (n = 37)	>10,000 (n = 36)	Tachycardia (n = 31)	<1,000 vs. 1,000-10,000 vs. >10,000 vs. Tachycardia	<1,000 vs. 1,000-10,000	<1,000 vs. >10,000	<1,000 vs. Tachycardia	1,000-10,000 vs. >10,000	1,000-10,000 vs. Tachycardia	>10,000 vs. Tachycardia
Age, years	15.5 [4.0]	15.2 [3.7]	13.7 [3.9]	13.5 [5.0]	0.27	0.45	0.13	0.11	0.29	0.27	0.60
Sex, M:K n(%)	10 (45.5):12 (54.5)	18 (48.6):19 (51.4)	19 (52.8):17 (47.2)	19 (61.3):12 (38.7)	0.66	1.0	0.79	0.28	0.82	0.34	0.62
BMI, kg/m²	19.1 [3.9]	20.5 [5.2]	19.5 [5.3]	18.0 [5.8]	0.70	0.70	0.92	0.34	0.58	0.35	0.42
Months from onset of the arrhythmia	12.0 [21.0]	3.0 [4.0]	12.0 [45.0]	12.0 [30.0]	0.002	0.02	0.53	0.43	0.004	0.0001	0.67
IL-6, pg/ml	1.43 [2.50]	0.78 [1.10]	1.10 [1.62]	0.97 [2.37]	0.73	0.35	0.85	0.95	0.38	0.39	0.87
CRP, mg/l	0.50 [0.24]	0.50 [0.69]	0.50 [0.10]	0.50 [0.60]	0.34	0.52	0.77	0.28	0.35	0.08	0.49
-174 G>C genotypes, GG:GC:CC	7 (31.8):10 (45.4):5 (22.7)	10 (27.0):18 (48.6):9 (24.3)	10 (27.8):19 (52.8):7 (19.4)	9 (29.0):14 (45.2):8 (25.8)	0.99 (GG vs. GC vs. CC), 0.98 (GG vs. GC+CC) 0.93 (GG+GC vs. CC)	0.93 (GG vs. GC vs. CC), 0.77 (GG vs. GC+CC) 1.0 (GG+GC vs. CC)	0.86 (GG vs. GC vs. CC), 0.77 (GG vs. GC+CC) 0.75 (GG+GC vs. CC)	0.96 (GG vs. GC vs. CC), 1.0 (GG vs. GC+CC) 1.0 (GG+GC vs. CC)	0.88 (GG vs. GC vs. CC), 1.0 (GG vs. GC+CC) 0.78 (GG+GC vs. CC)	0.96 (GG vs. GC vs. CC), 1.0 (GG vs. GC+CC) 1.0 (GG+GC vs. CC)	0.78 (GG vs. GC vs. CC), 1.0 (GG vs. GC+CC) 0.57 (GG+GC vs. CC)
174 G>C alleles, G:C; n (%)	24 (54.5):20 (45.4)	38 (51.4):36 (48.6)	39 (54.2):33 (45.8)	32 (51.6):30 (48.4)	0.98	0.85	1.0	0.84	0.74	1.0	0.86

BMI - body mass index; IL-6 - interleukin-6; CRP - C-reactive protein.

Table 1. **Characteristics of the study subgroups and the major results of the study.**

	Study subgroups			P-values			
	SV (n = 63)	**V (n = 63)**	**Controls (n = 37)**	**SV vs. V**	**SV vs. controls**	**V vs. controls**	**SV+V vs. controls**
Age, years	13.8 [5.1]	15.0 [3.4]	14.8 [5.6]	0.08	0.29	0.72	0.70
Sex, M:F; n(%)	34 (54.0):29 (46.0)	32 (50.8):31 (49.2)	21 (56.8):16 (43.2)	0.86	0.84	0.68	0.71
BMI, kg/m²	18.7 [5.5]	19.9 [4.9]	19.1 [4.9]	0.39	0.59	0.81	0.87
Time from the onset of the arrhythmia; months	12.0 [33.0]	5.0 [22.0]	n/a	0.19	n/a	n/a	n/a
IL-6, pg/mL	1.03 [1.80]	0.76 [1.47]	1.35 [1.73]	0.25	0.76	0.17	0.35
CRP, mg/L	0.50 [0.23]	0.50 [0.30]	0.50 [0.15]	0.52	0.96	0.50	0.72
-174 G>C genotypes, GG:GC:CC; n(%)	19 (30.2):32 (50.8):12 (19.0)	17 (27.0):29 (46.0):17 (27.0)	12 (33.3):15 (41.7):9 (25.0)*	0.57 (GG vs. GC vs. CC), 0.84 (GG vs. GC+CC) 0.40 (GG+GC vs. CC)	0.65 (GG vs. GC vs. CC), 0.82 (GG vs. GC+CC) 0.61 (GG+GC vs. CC)	0.80 (GG vs. GC vs. CC), 0.50 (GG vs. GC+CC) 1.0 (GG+GC vs. CC)	0.77 (GG vs. GC vs. CC), 0.68 (GG vs. GC+CC) 0.83 (GG+GC vs. CC)
-174 G>C alleles, G:C; n(%)	70 (55.6):56 (44.4)	63 (50.0):63 (50.0)	39 (54.2):33 (45.8)	0.45	0.88	0.66	0.89

SV - supraventricular arrhythmia; V - ventricular arrhythmia; BMI - body mass index; IL-6 - interleukin-6; CRP - C-reactive protein; n/a – not applicable.
**We failed to genotype one of the control subjects*

symptoms of prodromal airway infection and the spontaneous remission of arrhythmias was noted in 75% of the children. However, in the study by Wang and coauthors, inflammatory markers were not measured [28].

Our study addressed the issue of plausible differences in IL-6 and CRP along with –174 IL-6 polymorphism in pediatric patients with supraventricular versus ventricular arrhythmias. This study is the first to demonstrate that none of these factors differentiate children suffering from supraventricular versus ventricular arrhythmias when there were no AF cases and infections or inflammatory chronic diseases were excluded. It might be concluded that Il-6 and its polymorphism studied are similar regardless of the type of cardiac arrhythmias in children.

The study by Lefkou et al. [29] indicated that in children with a positive family history of coronary artery disease, low-grade inflammatory state typical of atherosclerosis begins early in childhood and the values of IL-6 and CRP in monocell cultures, as well as their plasma concentrations were significantly higher as compared to the controls. In the current study, none of the patients' parents or grandparents declared a positive history of coronary or cerebrovascular events. It seems unlikely that a positive family history of cardiovascular disease might explain cardiac arrhythmias in the present study.

This study has several limitations. First, the size of the study group and subgroups with various arrhythmias is limited, and the results of comparative analyses should be interpreted with caution. We cannot exclude that indeed AF in children is associated with elevated IL-6 as suggested in studies performed in adult patients [12-15]. AF is detected very rarely in children; therefore, in the present study, there were no AF cases. Second, all laboratory measurements were performed on a single occasion. Given various time intervals from the symptom onset, serial measurements might provide better insights into the role of IL-mediated inflammatory responses in cardiac arrhythmias in children. Third, we did not follow the children enrolled in this study to evaluate the risk for recurrent arrhythmias.

In summary, our results suggest that the selected pro-inflammatory markers i.e. serum IL-6, CRP or a common –174G>C IL-6 gene polymorphism are not involved in the pathogenesis of cardiac supraventricular or ventricular arrhythmias in children. Further studies are needed to investigate whether other inflammatory pathways might be implicated in arrhythmias in this age group.

CONCLUSIONS

The study revealed that in children diagnosed with supraventricular or ventricular arrhythmia, the values of selected pro-inflammatory markers i.e. serum IL-6, –174 G>C IL-6 polymorphism and CRP concentrations were normal. Also, severity of arrhythmias showed no associations with IL-6, CRP or –174 G>C IL-6 genotypes. It may suggest that idiopathic arrhythmias in children probably are not triggered or associated with infections. This new information can effectively reduce the total financial costs of unnecessary diagnosis and treatment of children–around the world–affected by cardiac arrhythmia.

REFERENCES

1. Vickers MA, Green FR, Terry C, Mayosi BM, Julier C, Lathrop M, Ratcliffe PJ, Watkins HC, Keavney B. Genotype at a promoter polymorphism of the interleukin-6 gene is associated with baseline levels of plasma C-reactive protein. Cardiovasc Res. 2002 Mar;53(4):1029-34.

2. Jones J, Chen LS, Baudhuin L, Peterson S, Harmsen WS, Zinsmeister AR, McConnell J, Sandborn WJ. Relationships between C-reactive protein concentration and genotype in healthy volunteers. Clin Chem Lab Med. 2009;47(1):20-5.

3. Kilpinen S, Hulkkonen J, Wang XY, Hurme M. The promoter polymorphism of the interleukin-6 gene regulates interleukin-6 production in neonates but not in adults. Eur Cytokine Netw. 2001 Mar;12(1):62-8.

4. Humphries SE, Luong LA, Ogg MS, Hawe E, Miller GJ. The interleukin-6 -174 G/C promoter polymorphism is associated with risk of coronary heart disease and systolic blood pressure in healthy men. Eur Heart J. 2001 Dec;22(24):2243–52.

5. Potaczek DP, Undas A, Nowakowski T, Szczeklik A. Association between inflammatory markers and the interleukin-6 -174 G/C polymorphism is abolished in peripheral arterial occlusive disease. Int Angiol. 2007 Dec;26(4):318-23.

6. Potaczek DP, Undas A, Celinska-Lowenhoff M, Szczeklik A. Interleukin-6 -174 G/C promoter polymorphism and effects of fenofibrate and simvastatin on inflammatory markers in hypercholesterolemic patients. Blood Coagul Fibrinolysis. 2006 Jan;17(1):35–8.

7. Antonicelli R, Olivieri F, Bonafè M, Cavallone L, Spazzafumo L, Marchegiani F, Cardelli M, Recanatini A, Testarmata P, Boemi M, Parati G, Franceschi C. The interleukin-6 -174 G>C promoter polymorphism is associated with a higher risk of death after an acute coronary syndrome in male elderly patients. Int J Cardiol. 2005 Sep 1;103(3):266-71.

8. Jenny NS, Tracy RP, Ogg MS, Luong le A, Kuller LH, Arnold AM, Sharrett AR, Humphries SE. In the elderly, interleukin-6 plasma levels and the -174G>C polymorphism are associated with the development of cardiovascular disease. Arterioscler Thromb Vasc Biol. 2002 Dec 1;22(12):2066-71.

9. Sie MP, Sayed-Tabatabaei FA, Oei HH, Uitterlinden AG, Pols HA, Hofman A, van Duijn CM, Witteman JC. Interleukin 6 -174 g/c promoter polymorphism and risk of

coronary heart disease: results from the rotterdam study and a meta-analysis. Arterioscler Thromb Vasc Biol. 2006 Jan;26(1):212-7.

10. Cheng T, Wang XF, Hou YT, Zhang L. Correlation between atrial fibrillation, serum amyloid protein A and other inflammatory cytokines. Mol Med Report. 2012 Sep;6(3):581-4.

11. Psychari SN, Chatzopoulos D, Iliodromitis EK, Apostolou TS, Kremastinos DT. C-reactive protein, interleukin 6, and N-terminal pro-brain natriuretic peptide following cardioversion of atrial fibrillation: is there a role of biomarkers in arrhythmia recurrence? Angiology. 2011 May;62(4):310-6.

12. Smit MD, Maass AH, De Jong AM, Muller Kobold AC, Van Veldhuisen DJ, Van Gelder IC. Role of inflammation in early atrial fibrillation recurrence. Europace. 2012 Jun;14(6):810-7.

13. Masson S, Aleksova A, Favero C, Staszewsky L, Bernardinangeli M, Belvito C, Cioffi G, Sinagra G, Mazzone C, Bertocchi F, Vago T, Peri G, Cuccovillo I, Masuda N, Barlera S, Mantovani A, Maggioni AP, Franzosi MG, Disertori M, Latini R; GISSI-AF investigators. Predicting atrial fibrillation recurrence with circulating inflammatory markers in patients in sinus rhythm at high risk for atrial fibrillation: data from the GISSI atrial fibrillation trial. Heart. 2010 Dec;96(23):1909-14.

14. Patel P, Dokainish H, Tsai P, Lakkis N. Update on the association of inflammation and atrial fibrillation. J Cardiovasc Electrophysiol. 2010 Sep;21(9):1064-70.

15. Marcus GM, Smith LM, Ordovas K, Scheinman MM, Kim AM, Badhwar N, Lee RJ, Tseng ZH, Lee BK, Olgin JE. Intracardiac and extracardiac markers of inflammation during atrial fibrillation. Heart Rhythm. 2010;7(2):149-54.

16. Li J, Solus J, Chen Q, Milne G, Stein CM, Darbar D. Role of inflammation and oxidative stress in atrial fibrillation. Heart Rhythm. 2010 Apr;7(4):438-44.

17. Shah SS, Hellenbrand WE, Gallagher PG. Atrial flutter complicating neonatal Coxsackie B2 myocarditis. Pediatr Cardiol. 1998 Mar-Apr;19(2):185-6.

18. Grosse-Wortmann L, Muehler EG. Myocardial ischaemia in a child infected with influenza B. Cardiol Young. 2005 Apr;15(2):226-8.

19. Abrams D, Derrick G, Penny DJ, Shinebourne EA, Redington AN. Cardiac complications in children following infection with varicella zoster virus. Cardiol Young. 2001 Now;11(6):647-52.

20. Steininger C, Holzmann H, Zwiauer KF, Popow-Kraupp T. Influenza A virus infection and cardiac arrhythmia during the neonatal period. Scand J Infect Dis. 2002;34(10):782-4.

21. Raza MW, Blackwell CC. Sudden infant death syndrome, virus infections and cytokines. FEMS Immunol Med Microbiol. 1999 Aug1;25(1-2):85-96.

22. Huang M, Bigos D, Levine M. Ventricular arrhythmia associated with respiratory syncytial viral infection. Pediatr Cardiol. 1998 Nov-Dec;19(6):498-500.

23. Schultz JC, Hilliard AA, Cooper LT, Rihal CS. Diagnosis and treatment of viral myocarditis. Mayo Clin Proc. 2009 Nov;84(11):1001-9.

24. Simpson KE, Hulse E, Carlson K. Atrial tachyarrhythmias in neonatal enterovirus myocarditis. Pediatr Cardiol. 2009 Aug;30(6):827-30.

25. Kühl U, Schultheiss HP. Myocarditis in children. Heart Fail Clin. 2010 Oct;6(4):483-96, viii-ix.

26. Kowalewski M, Urban M, Mroczko B, Szmitowski M. Cytokiny prozapalne (IL-6, TNF-ŕ) i sercowa troponina I (cTnI) w surowicy mlodych osob z komorowymi zaburzeniami rytmu serca [Proinflammatory cytokines (IL-6, TNF-alpha) and cardiac troponin I (cTnI) in serum of young people with ventricular arrhythmias] Pol Arch Med Wewn. 2002 Jul;108(1):647-51. Polish.

27. Beaufort-Krol GC, Dijkstra SS, Bink-Boelkens MT. Natural history of ventricular premature contractions in children with a structurally normal heart: does origin matter? Europace. 2008 Aug;10(8):998-1003.

28. Wang JN, Wu JM, Tsai YC, Lin CS. Ectopic atrial tachycardia in children. J Formos Med Assoc. 2000 Oct;99(10):766-70.

29. Lefkou E, Fragakis N, Ioannidou E, Bounda A, Theodoridou S, Klonizakis P, Garipidou V. Increased levels of proinflammatory cytokines in children with family history of coronary artery disease. Clin Cardiol. 2010 Apr;33(4):E6-10.